A STUDY ON "CORRELATION OF THYROID PROFILE WITH THE COMPONENTS OF METABOLIC SYNDROME"

Dissertation submitted in partial fulfillment of Requirement

For the award of the Degree of

DOCTOR OF MEDICINE - BRANCH VII

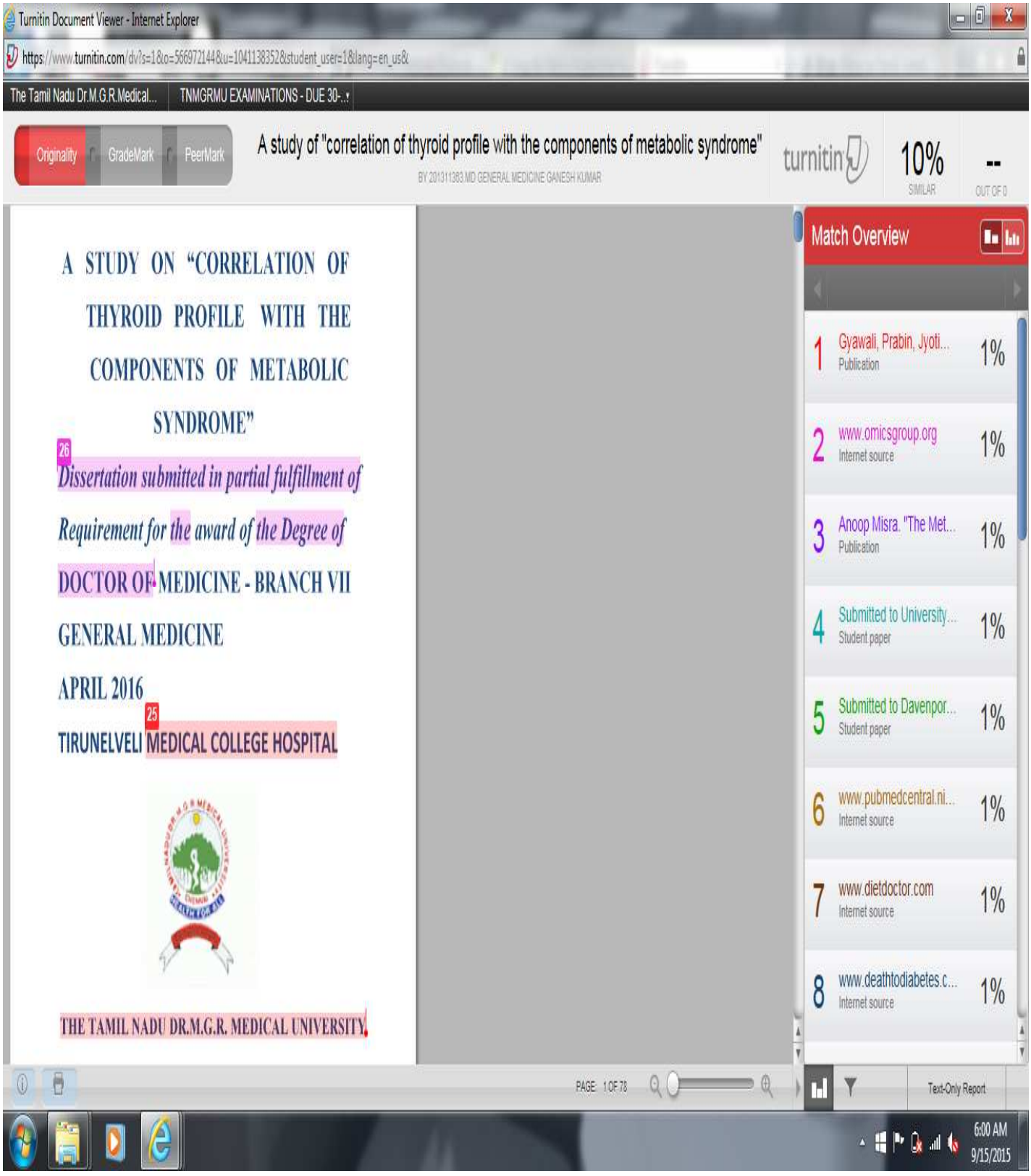
GENERAL MEDICINE

APRIL 2016

TIRUNELVELI MEDICAL COLLEGE HOSPITAL.

THE TAMIL NADU DR.M.G.R. MEDICAL UNIVERSITY

CHENNAI, TAMIL NADU.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CERTIFICATE OF REGISTRATION & APPROVAL OF THE TIREC REF NO: 535/GM/2014/42

PROTOCOL TITLE: A STUDY OF "CORRELATION OF THYROID PROFILE WITH THE COMPONENTS OF METABOLIC SYNDROME".

NAME OF PRINCIPAL INVESTIGATOR: Dr. P. Ganesh Kumar, MBBS.,
DESIGNATION OF PRINCIPAL INVESTIGATOR: Post Graduate in MD General Medicine
DEPARTMENT & INSTITUTION: Department of General Medicine, Tirunelveli Medical College

Dear Dr. P.Ganesh Kumar, The Tirunelveli Medical College Institutional Ethics Committee (TIREC) reviewed and discussion your application during the IEC meeting held on 14.03.14.

THE FOLLOWING DOCUMENTS WERE REVIEWED AND APPROVED

1.	TIREC Application Form	☐
2.	Study Protocol	☐
3.	Department Research Committee Approval	☐
4.	Patient Information Document and Consent Form in English and Vernacular Language	☐
5.	Investigator's Brochure	☐
6.	Proposed Methods for Patient Accrual Proposed	☐
7.	Curriculum Vitae of the Principal Investigator	☐
8.	Insurance /Compensation Policy	☐
9.	Investigator's Agreement with Sponsor	☐
10.	Investigator's Undertaking	☐
11.	DCGI/DGPT approval	☐
12.	Clinical Trial Agreement (CTA)	☐
13.	Memorandum of Understanding [MOU]/Material Transfer Agreement (MTA)	☐
14.	Clinical Trials Registry-India (CTRI) Registration	☐

THE PROTOCOL IS APPROVED IN ITS PRESENTED FORM ON THE FOLLOWING CONDITIONS

1. The approval is valid for a period of 2 year/s or duration of project whichever is later
2. The date of commencement of study should be informed
3. A written request should be submitted 3weeks before for renewal / extension of the validity
4. An annual status report should be submitted.
5. The TIREC will monitor the study
6. At the time of PI's retirement/leaving the institute, the study responsibility should be transferred to a person cleared by HOD
7. The PI should report to TIREC within 7 days of the occurrence of the SAE. If the SAE is Death, the Bioethics Cell should receive the SAE reporting form within 24 hours of the occurrence.
8. In the events of any protocol amendments, TIREC must be informed and the amendments should be highlighted in clear terms as follows:
   a. The exact alteration/amendment should be specified and indicated where the amendment occurred in the original project. (Page no. Clause no. etc)
   b. The PI must comment how proposed amendment will affect the ongoing trial. Alteration in the budgetary status, staff requirement should be clearly indicated and the revised budget form should be submitted.
   c. If the amendments require a change in the consent form, the copy of revised Consent Form should be submitted to Ethics Committee for approval. If the amendment demands a re look at the toxicity or side effects to patients, the same should be documented.
   d. If there are any amendments in the Trial design, these must be incorporated in the protocol, and other study documents. These revised documents should be submitted for approval of the IEC, only then can they be implemented.
   e. Approval for amendment changes must be obtained prior to implementation of changes.
   f. The amendment is unlikely to be approved by the IEC unless all the above information is provided
   g. Any deviation/violation/waiver in the protocol must be informed

STANDS APPROVED UNDER SEAL

Dr.R.Shanthakumar MD
Registrar, TIREC
Tirunelveli Medical College, Tirunelveli – 627011
State of Tamilnadu, South India

Dr.V.Ramasubramanian MD DM
Member Secretary, TIREC
Tirunelveli Medical College, Tirunelveli – 627011
State of Tamilnadu, South India

CERTIFICATE

This is to certify that the Dissertation entitled a study on **"CORRELATION OF THYROID PROFILE WITH THE COMPONENTS OF METABOLIC SYNDROME"** submitted by **Dr.P. GANESH KUMAR** to The Tamilnadu Dr. M.G.R. Medical University, Chennai, in partial fulfillment for the award of M.D.Degree(GENERAL MEDICINE) is a bonafide work carried out by him under my guidance and supervision during the academic year 2013-2016. This dissertation partially or fully has not been submitted for any other degree or diploma of this university or other.

Prof.Dr.RAVICHANDRAN. MD.,
Chief, UNIT III,
Department of Medicine,
Tirunelveli Medical College ,
Tirunelveli – 627011.

Prof. Dr.VAIRAMUTHURAJU. MD
Professor and HOD,
Department of Medicine,
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Dr. SITHI ATHIYA MUNAVARAH M.D
The Dean,
Tirunelveli Medical College,
Tirunelveli – 627 011.

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DECLARATION

I**, Dr.P.GANESH KUMAR,** solemnly declare that the Dissertation titled **"A STUDY ON CORRELATION OF THYROID PROFILE WITH THE COMPONENTS OF METABOLIC SYNDROME "** has been prepared by me. This is submitted to the Tamilnadu Dr.M.G.R. Medical University, Chennai, in partial fulfillment of the regulations for the award of MD Degree Branch VII (MEDICINE).

It was not submitted to the award of any degree/diploma to any University either in part or in full previously.

PLACE: TIRUNELVELI

DATE :

Dr.P.GANESH KUMAR,

POST GRADUATE,

M.D.GENERAL MEDICINE,

TIRUNELVELI MEDICAL COLLEGE.

ACKNOWLEDGEMENT

At the outset I wish to thank our beloved Dean Dr. SITHI ATHIYA MUNAVARAH M.D , for permitting me to carry out this study in our hospital. I express my sincere thanks to my Professor and HOD Dr.VAIRAMUTHU RAJU. MD, for his support and encouragement throughout the study. I am also deeply indebted to my chief Prof Dr.RAVICHANDRAN. MD , who was the main motivator behind the study & suggested the topic. I am thankful to my assistant professors Dr.THOMAS KINGSLY.MD, Dr.SANKARA NARAYANAN.MD and Dr. RAJESH BABU MD., for their valuable suggestions, encouragement and valuable guidance to the study. I am also immensely grateful to my statistician, Mr.SELVAPRAKASAM, for the guidance he provided in the analysis and interpretation of the data. I also thank the Department of Biochemistry, for the laboratory support to this study. Last but not the least, I sincerely thank all the patients who cooperated with me by participating in the study.

CONTENTS

INTRODUCTION

Need for the study:

Metabolic syndrome has affected more than 25% of the population in the western civilisations. MetS is a major determining factor for the early onset of insulin resistant diabetes & accelerated atherosclerosis. MetS is clinically a conglomeration of risk factors highlighted by the presence of systemic hypertension, altered lipid profile, dysglycemia, proinflammatory & prothrombotic states.

Sub-clinical hypoT & MetS are well established risk factors for atheromatous-occlusive vascular diseases, dyslipidemia, low grade persistent inflammatory state and pro-coagulable state. This association may be in part be explained by thyroid hormone's regulatory effect on lipid metabolism and blood pressure.

MetS and sub-clinical/overt thyroid dysfunction are independent risk factors, in the genesis of cardiovascular diseases. Hence, it is plausible that persons affected with both these conditions, could have more than additive hazard.

This study is a step towards ascertaining the possible positive link of thyroid dysfunction with the components of MetS.

In this study, TSH has been used as the prime indicator of thyroid dysfunction, as it increases before the elevation of FT4 and also before clinical manifestation.

Review of literature:

In a study conducted by Texas University, involving greater than 1,600 adults, investigators noticed that persons with MetS have statistically significant serum TSH levels in comparison to healthy control population. In addition, subclinical hypoT was found to be positively associated with increased TGL levels & elevated blood pressure. On the other

hand, modest increase in TSH could place people at excess risk for development of MetS.

Several studies have shown a significant association which links metabolic syndrome with subclinical and overt hypothyroidism and the association seems to be more in females. Uzunlulu et al reported that the prevalence of subclinical hypothyroidism was greater in women with MetS.

In a study by Bauer DC et al, it was concluded that among older hispanic women, elevated TSH levels were associated with hazardous changes in composition of lipids & that women with multitude lipid abnormalities were thrice as likely to have increased TSH levels.

The study conducted by Tromso and Basel, has proven that thyroxine supplementation, in patients with borderline thyroid dysfunction, has a better effect on low density(LDL) cholesterol values. This also led to relative risk reduction in cardiovascular morbidity of 9–31%. This benefit being attributed to observed reduction in serum low density(LDL) cholestrol levels.

A study conducted by HUNT, proposed that "Within the range of TSH that is considered clinically normal, increasing level of TSH was associated with less favorable lipid concentrations. The association with serum lipids was linear across the entire reference range of TSH".

Research published in the February 2007 issue of the "*Journal of Clinical Endocrinology and Metabolism*" found a connection between thyroid function & metabolic syndrome. In euthyroid persons ie TSH within normal levels, the level of free T4 was important. Free T4 levels that were slightly low, but still within the normal range, significantly increased the risk of many risk factors for metabolic syndrome.

In hypothyroidism , energy metabolism is reduced leading to a decreased in appetite , cold intolerance, reduced protein synthesis , lipid accumulation(elevated TG and LDL-Cholesterol).

Study by L.Chandra et al revealed a varied effect of thyroid status on the components of metabolic syndrome. The observed changes are statistically significant within and between

euthyroid , hypothyroid , hyperthyroid having metabolic syndrome and the group not having metabolic syndrome.

In a study conducted by Banaras University, atherogenic lipid abnormalities were observed in adult subjects with Subclinical hypothyroidism-2 (TSH > 10.0 Miu/L), and not in subjects with Subclinicalhypothyroidism-1 who had TSH ≤ 10.0 Miu/L in Indian population.

The Jaipur Heart Watch Study has shown that in urban adult populations, the prevalence of MetS was nearly 19% in men, 30% in women, and approximately 25% on the whole.

As per the CURES 52 study, elevated BP is evident in around one-fifth of the population in chennai. Amidst those hypertensive patients, the presence of other defining characters of MetS was: type2-diabetes in 31.8%, IGT in 17.9%, dys-lipidemia in 38.8%, hypertriglyceridemia in 38%, high visceral adiposity in 64.3% and high BMI in 40%.

In a population based study conducted by, "Prevention of Metabolic Disorders Research Center, Iran", of over 900 reproductive aged women, subclinical thyroid dysfunction was found to be significantly related with two components of MetS- low HDL and high TGL. In addition, the average estimated total score of MetS in women with SCH was significantly higher than the euthyroid women. This has been also observed that TSH levels were negatively correlated with HDL-C and positively with diastolic blood pressure independently of well-known MetS risk factors.

Metabolic Syndrome

Metabolic syndrome is characterised by accumulation of multiplex of risk factors that roots from insulin resistance, henceforth accompanied by abnormal adipose tissue deposition and function.

This is one of the most important problems faced by the modern fraternity in the last two and half decades.

Problem statement:

- About 25% of the world's adult population has metabolic syndrome.
- People with metabolic syndrome three times as likely to have a heart attack or stroke compared with people without the syndrome.
- People with metabolic syndrome have a five-fold greater risk of developing type 2 diabetes.
- People with metabolic syndrome two times as likely to have a cardio vascular mortality, as compared with people without the syndrome.
- This puts metabolic syndrome way ahead as a giant killer disease, yet the problem is not as well recognised.

Hence earlier diagnosis is needed to stop this global time bomb.

HISTORY:

Long before the modern definition of MetS, the Italian physician, Morgagni, described the association between visceral obesity, arterial hypertension, atherosclerosis and high levels of uric acid in blood, almost 250 years ago.

In 1920, Nicolae Pautescu, suggested diabetes and obesity as the consequent phases of same pathological phases. In 1988, Reaven G., an endocrinologist, interpreted the association of diabetes mellitus, hypertension and dyslipidemia, by their pathogenic relationship with peripheral insulin resistance. He named this "Syndrome X".

Ferranini et al, confirmed this association and named it 'Insulin resistance syndrome'. Soon metabolic disturbances, was found to be involving larger spectrum. Zimmet & co, put forward "Syndrome X Plus", associated with sedentary life style,

hyperuricemia, obstructive sleep apnea etc. In 1998, WHO formulated the first official definition of MetS.

IDF definition:

For a person to be diagnosed to have MetS, he/she should have,

Central obesity, defined as waist circumference with ethnic specificity, >90cm for asian men and >80cm for asian women.

Plus any two of the following criteria

Raised triglycerides

> 150 mg/Dl (1.7 mmol/L)

(Or) on specifi c treatment for this lipid abnormality

Reduced HDL cholesterol

< 40 mg/Dl (1.03 mmol/L) in males

< 50 mg/Dl (1.29 mmol/L) in females

(Or) on specifi c treatment for this lipid abnormality

Raised blood pressure

Systolic BP 130mm of Hg & above

(or) Diastolic BP 85 mm Hg & above

(or) 0n treatment of previously diagnosed hypertension

Raised fasting blood sugar

FPG > 100 mg/Dl (5.6 mmol/L),

(or) previously diagnosed type 2 diabetes

If above 5.6 mmol/L or 100 mg/Dl, OGTT is strongly recommended but is not necessary to define presence of the syndrome.

Prevalence:

The exact prevalence varies according to extent of westernisation, lifestyle patterns and economic & cultural patterns prevailing in the area. Indian studies have shown that the prevalence is more than 30% in urban population and is still swelling. Gender difference is significant, with the women leading the charts. Prevalence is 1.5- 2 times higher in women compared to men.

There has been, also, a recent surge in prevalence among the rural Indian population. Alarming increasing childhood obesity rates, is a cause for concern. These factors indicate the menace, we are about to face in the near future.

Risk factors for MetS:

Ethnicity

Asian Indian phenotype, is predisposed to the development of MetS. This is characterised by higher body fat with comparatively, lower BMI. The proportion of intra-abdominal visceral fat is much higher compared to lean body mass, in asian adults. Hence asian phenotype, has higher prevalence, earlier onset and increased complications of T2DM at lower BMIs.

Obesity

Higher the body weight, higher the prevalence and risk of development of MetS. Increased waist circumference is a positive predictor of future development of MetS.

DIET

There has been a decline in the intake of traditional foods, in the recent two to three decades. Traditional Indian foods had higher fibre content and was lower in simple sugars and saturated fat. The food composition has varied a lot now-a-days. Higher consumption of animal fats, dairy products and hydrogenated oils, has been shown to have a higher correlation with the development of cardiovascular diseases. These changes in dietary patterns may be implicated in the increased incidence of metabolic syndrome.

Physical activity

Increased mechanisation of work, increased indoor entertainment activities and reduced outdoor activity, has resulted in decreased physical activity on the whole. Finally resulting in increased weight and waist circumference.

Migration

An adverse coronary risk profile has been reported among rural-to-urban migrant population. This has been suggested due to significant stress arising out of new environment, job challenges, socio-economic disparities, lack of social support etc.

Genetic and environmental factors

Adverse intrauterine environment, has been linked to insulin resistance and metabolic syndrome. Low birth weight is associated with high SBP, insulin resistance, fasting hyperinsulinemia. Catch up obesity seen in LBW offspring seems to be important for adult onset insulin resistance and associated cardiovascular risk factors.

Psychological factors

Stress activates sympathetic nervous system leading to hormonal fluctuations. Stress has been associated with hypertension, which is an integral part of metabolic syndrome.

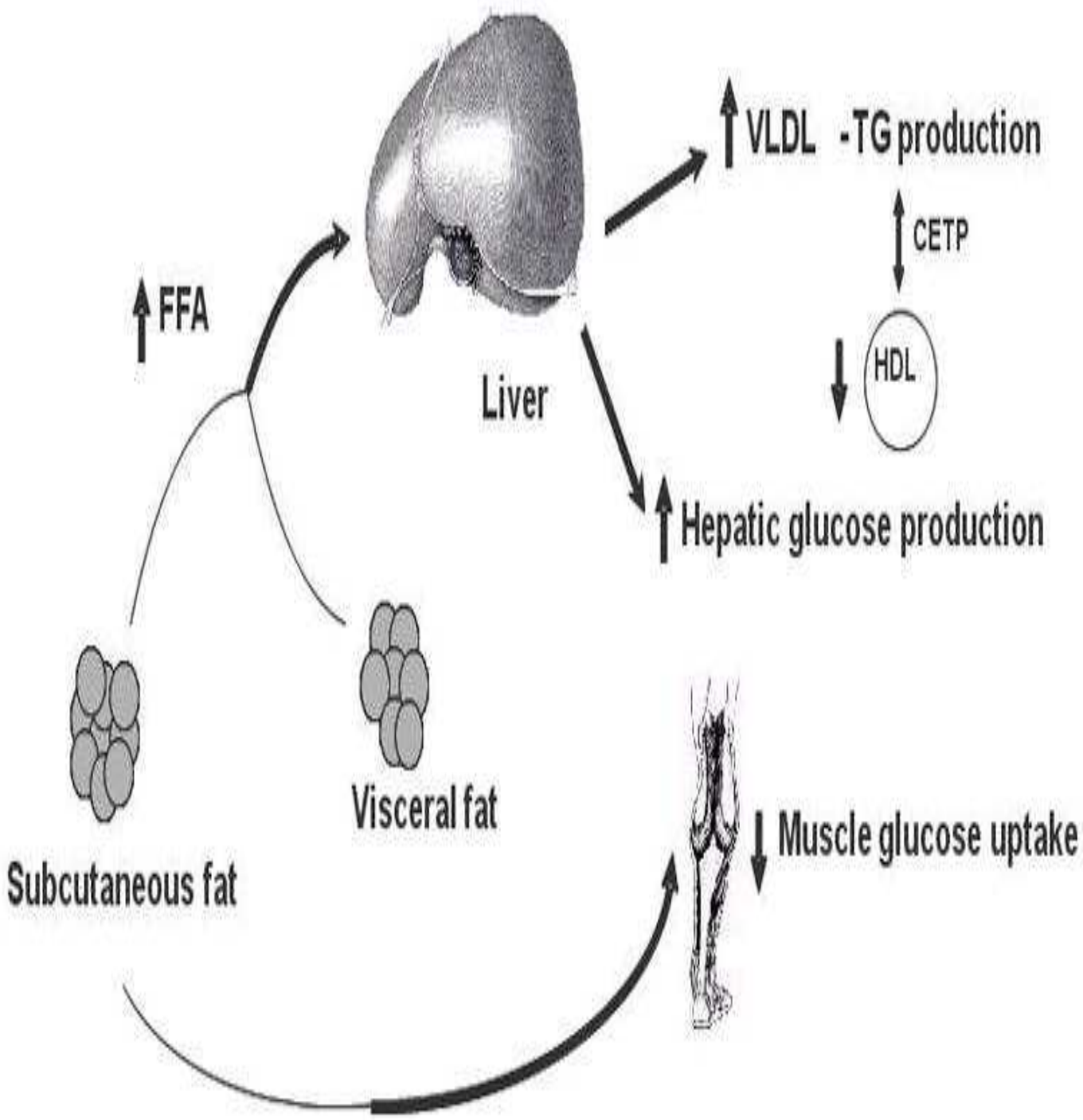
Pathophysiology

Resistance to the action of insulin is the corner stone for the altered metabolic state of the MetS. Altered free fatty acid metabolism is the prime component involved in the pathophysiology of dysglycemia and hyperlipidemia. Increased plasma FFA concentration impairs the ability of insulin to stimulate muscle glucose uptake and suppress hepatic glucose production. In addition, high levels of free fatty acids delivered to the liver increases hepatic very-low density lipoprotein triglyceride production and plasma triglyceride concentration. An increase in plasma triglycerides increases the transfer of triglyceride from VLDL to high density lipoprotein, resulting in increased high

density lipoprotein clearance & decreased serum high density lipoprotein(HDL) levels.

Adipose tissue secretes many pro-inflammatory mediators (adipokines). These result in resistance to insulin action. For example, TNF-alpha reduces insulin signaling, IL-6 increases inflammatory reaction directly & stimulates hepatic-CRP production, MCP-1 is a strong chemotactant for macrophages , and IL-8 is activator for neutrophil granulocytes & chemoattractant for most of the described migrating immune cells. This chronic inflammatory process leads to heightened insulin resistance.

Excessive intrahepatic steatosis is associated with impaired hepatic insulin action. This also cause reduced insulin-dependent suppression of nocturnal glucose release from liver. Excessive muscle fat is related to insulin resistance. This also impairs insulin-dependent glucose disposage.



Pictorial representation of pathogenesis of MetS

MetS and CVD risk:

Overall, the metabolic syndrome is associated with a two-fold increase in risk of CVD, CVD mortality, and stroke. There has been also a 1.5-fold increase in risk of all-cause mortality. Patients with the metabolic syndrome, but without type 2 diabetes mellitus, are still at high risk for CVD mortality, MI, and stroke. The metabolic syndrome does not require type 2 diabetes mellitus in order to be closely associated with cardiovascular risk.

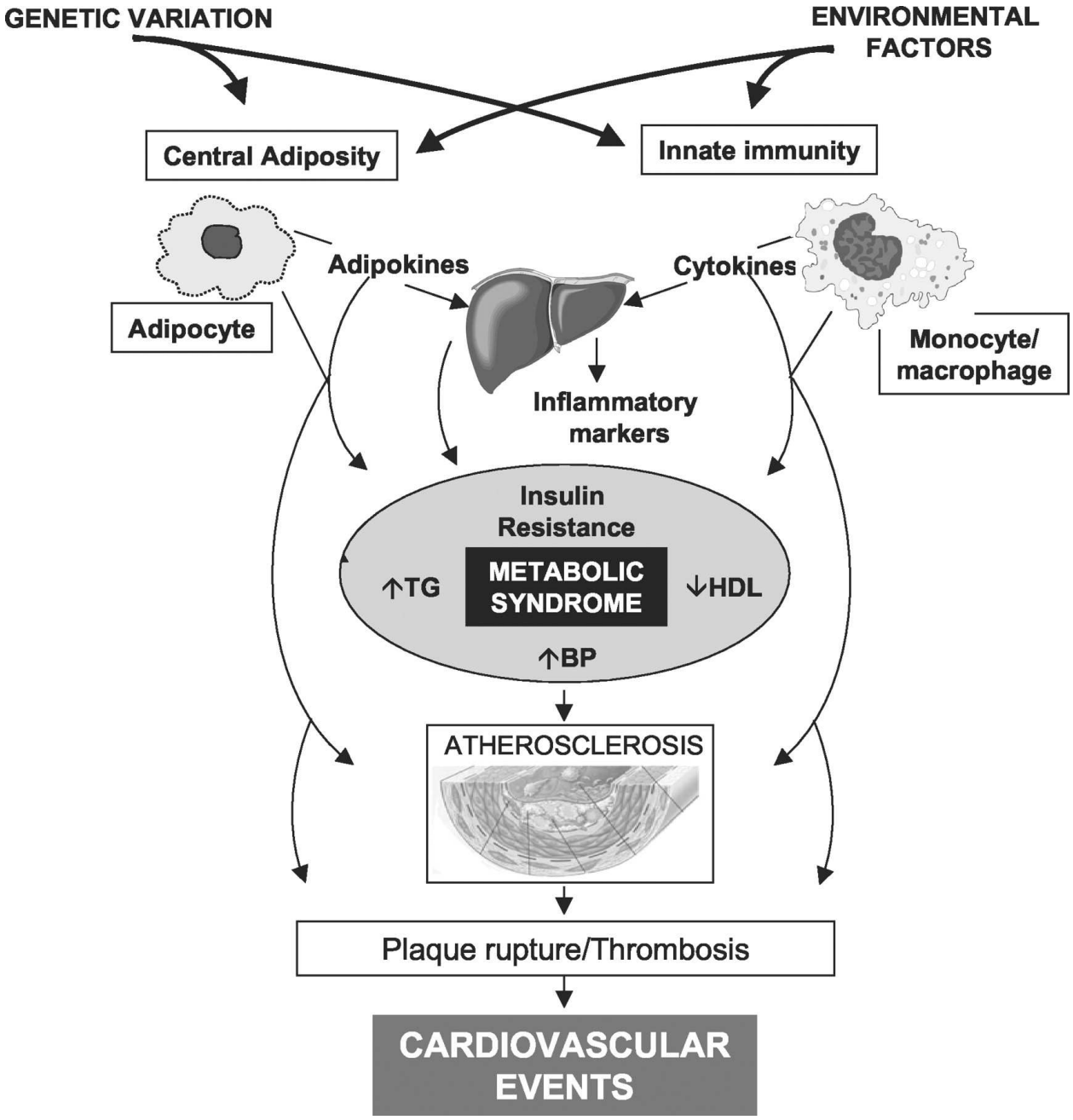
Many meta-analyses have shown that the metabolic syndrome is associated with higher cardiovascular risk in women relative to men. Several theories have been postulated to explain a potentially higher cardiovascular risk in women with the metabolic syndrome .

1) central adiposity tends to be more pronounced in postmenopausal women than in men.

2) The cholesterol profile is different in women compared with men. HDL cholesterol decreases and LDL cholesterol Increases post-menopausally. Also LDL particles becoming denser, and therefore, more atherogenic.

3) Elevated triglycerides are more highly associated with coronary artery disease in women than in men. In a meta-analysis, it was shown that an increase in triglycerides of 18 mg/dl was associated with a 76% increased cardiovascular risk in women compared with a 32% increased risk in men .

4) Presence of other unique risk factors like polycystic ovary syndrome, hormonal contraceptive use, and gestational diabetes may be responsible for a stronger association between the metabolic syndrome and cardiovascular risk in women.
The key mechanism behind elevated CVD risk is attributable to the proinflammatory and prothrombotic state associated with MetS.


GENETIC VARIATION
ENVIRONMENTAL FACTORS
Central Adiposity
Innate immunity
Adipokines
Cytokines
Adipocyte
Monocyte/ macrophage
Inflammatory markers
Insulin Resistance
↑TG
METABOLIC SYNDROME
↓HDL
↑BP
ATHEROSCLEROSIS
Plaque rupture/Thrombosis
CARDIOVASCULAR EVENTS

Pro-inflammatory state:

Insulin resistance and obesity have been closely linked to a pro-inflammatory condition. The main reason being excessive cytokine synthesis & release of acute phase reactants. C-Reactive protein is one of the important acute phase reactant, mainly produced in liver, after any noxious stimuli. Data from prior scientific researches have shown an association between serum CRP levels and features of MetS . CRP levels closely predicts the development of T2DM and Cardio-vascular diseases.

The liver being prime reign of systemic inflammatiory process, chronic exposure to pro-inflammatory mediators occurs. This results in excess production of many of the acute phase reactants, like CRP. Persistent low level inflammation noticed in obese population, causes persistent elevation of pro-inflammatory mediators. The major mediators are TNF-α, IL-6, and IL-8. All these inflammatory mediators induce resistance to

insulin action, the prime target being hepatic tissue and muscles.

Pro-coagulant state

Pro-coagulant state is being an important ally of MetS. Many factors have been suggested to be associated in hemostasis regulation in MetS. The main haematologic abnormality associated with MetS is the excessive levels of Plasminigen activator inhibitor-1. It is the important suppressor of fibrinolysis. Community level studies have concluded that excessive levels of PAI-1 is a fore-teller of myocardial ischaemia & CV mortality. Hepatic fat accumulation is the major reason for increased plasma PAI-1 levels in persons having MetS.

MetS is related to excessive amount of plasma fibrinogen, factor-7 & factor 8. This leads to the procoagulable condition. Fibrinogen, being acute-phase reactant, is produced by the hepatic tissue. Elevated levels of serum fibrinogen is related to

both the chronic persistent inflammatory process & resistance to insulin in MetS.

Even-then, the exact mechanism behind the excess production of fibrinogen from the hepatic tissue is yet to be cleared. This has been proposed that Free fatty acids and inflammatory mediators linked to insulin resistance, promote the hepatic production of clotting factors.

Pro-atherosclerotic state:

Fattyacid binding proteins by integrating metabolic & immune responses, interlink the inflammatory and lipid-mediated pathways. This mechanism plays a vital role in MetS. Thus FABPs are causative in the process of atherosclerosis , mainly by modifying cholesterol trafficking & inflammatory processes. The FABPs thus, implicate a longlasting impact on visceral adiposity, insulin resistance, diabetes mellitus & Non-alcoholic fatty liver disease.

Thus, MetS is a pro-inflammatory, pro-coagulant and pro-atherosclerotic state, resulting in elevated cardiovascular risk.

Management of MetS:

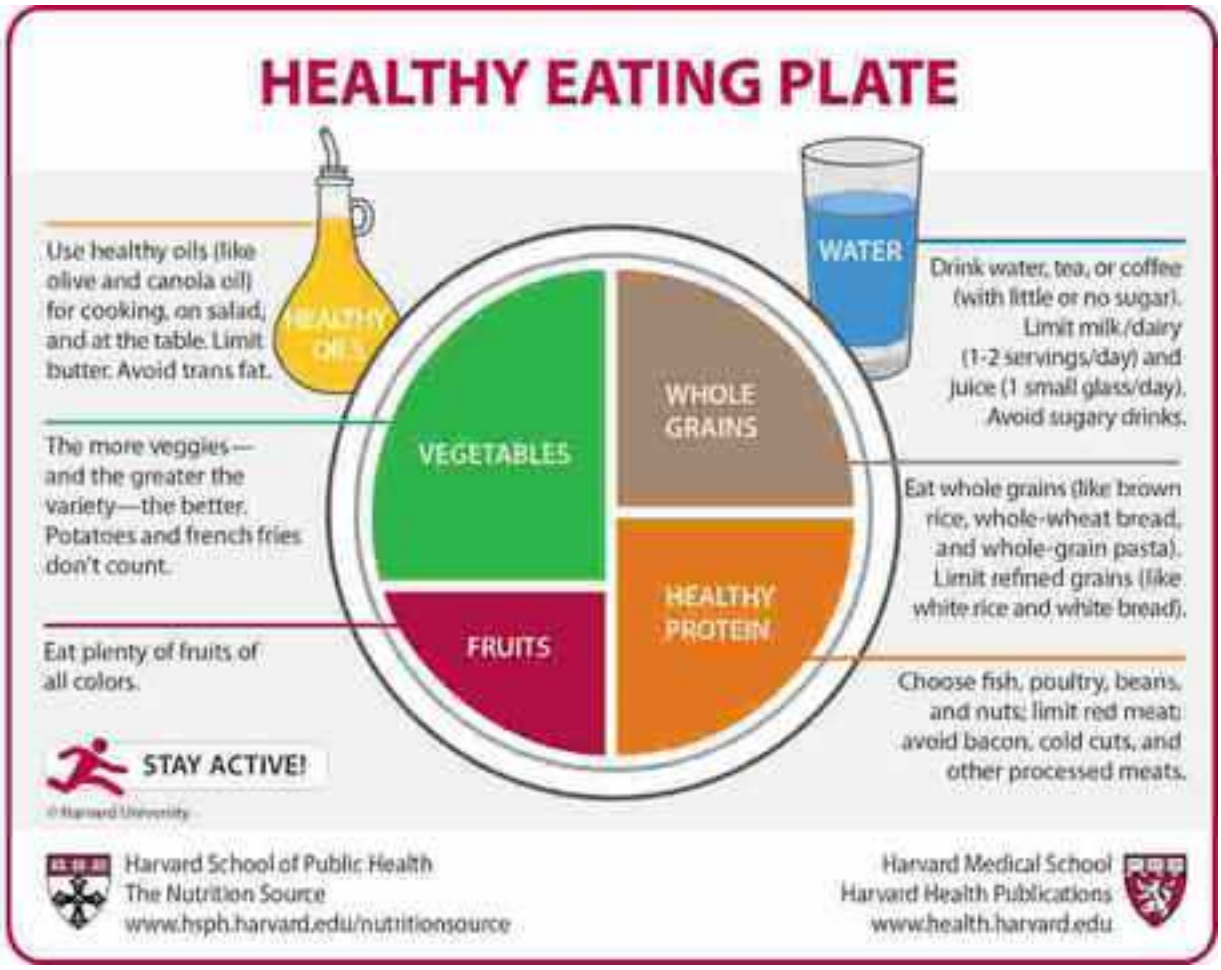
The efficient treatment, involves optimal control of the risk factors promoting development of MetS. By implementing lifestyle interventions remains the cornerstone of management. Intensive life-style changes involving diet and physical activity, is the recommended first-line treatment. Pharmacological therapy is advised, when the lifestyle changes do not produce optimal response. Pharmacological therapy, is needed in persons with a cardiovascular risk score more than 20% .

Life style modifications:

Most of the persons with MetS are either obese or overweight. They have to undergo a weight losing program. . A optimal achievable target is a 6% to 10% weight reduction over a period of six to nine months.

Adult Treatment Panel III suggests a well balanced diet, with reduced consumption of refined and simple sugars. T*rans* fatty acids have to be avoided. Fresh fruits, vegetables, and whole grains have to be consumed in large proportions. Nutritionists have suggested, a daily reduction of about 500–1000 kCal is the easiest way for a continued weight reduction, along with a well-scheduled, well-adhered phsical activity programme.

The most recent AHA recommendations, suggest a moderate intensity exercise regimen, for atleast a period of not less than thirty mts. Brisk walking and bicycling are the most favored exercise programme. All the sedentary activities in our daily routine life has to be avoided. Whenever possible, healthy lifestyle habits have to be adopted, for example, going to shopping by walk, utilizing steps instead of using lifts/travellators. All these have to be made a daily routine.



Specific Management of Metabolic Risk Factors:

. The exact objective of treating MetS is to decrease the heightened risk of cardiovascular diseases & to slow down the development of diabetes mellitus. A multitude of residual ongoing pathologic changes happening in MetS have to be answered. This may not be achieved even after, optimizing, life-style changes. In

these circumstances, pharmacological therapy, with a combination of drugs, is necessary.

Pharmocologic interventions:

Metformin, TZDs – for dysglycemia management.

Fibrates &statins – for dyslipidemia and pleiotropic effects.

ACEI/ARBs - for BP control and micro angiopathy protection.

Aspirin - for negating the procoagulant state.

Insulin resistance and glucose intolerance:

Insulin resistance associated with impaired glucose tolerance and elevated blood sugar levels is the hallmark feature of MetS. Hence treatment of insulin insensitivity can modify both glucose intolerance and dyslipidemia. A dietary pattern with a

reduction in simple sugars & saturated fats, in hands with easily adoptable exercise program is the main modality of therapy .

Drugs that enhance insulin sensitivity, like the biguanides (metformin) and the thiazolidenediones, (PPAR γ agonists), have the efficiency to either slowdown/ prevent the development of diabetes mellitus. These drugs also help in modifying the metabolic profile. Thus they decrease risk of atherosclerosis.

In a Diabetes Prevention Study conducted in Finland, a total of 522 persons with MetS, rigourous lifestyle modifications decreased the risk of diabetes to 58% , in comparison to the controls. In the DPP study, metformin in the dosage of 850 mg bid decreased the development of diabetes mellitus by 31%. In the same study, vigorous lifestyle changes reduced the risk to 58% in comparison to placebo. Inspite of earlier encouraging results, these drugs did not show any

reduction in risk of CVD. Hence such drugs should not be prescribed for the sole purpose of prevention.

Dyslipidemia:

Lifestyle intervention with dietary changes and physical activity is the prime therapy of dyslipidemia in the MetS. Eventhough raised Low Density cholesterol is a non-defining aspect of the lipid constitution in these patients, LDL-C and apo-B lipoproteins are pro-atherosclerotic. LDL reduction therapy has to be as per the cardiovascular risk score.

-in persons with ≥20% risk as calculated by the presence of CAD or CAD risk equivalents, the desired LDL level is less than 100 mg/Dl.

-patients with medium risk ie 10 – 20% have to achieve a desired LDL level <130mg/dl.

In persons with elevated TGL levels, more than 200 mg/dl, increased quantity of pro-atherosclerotic remnant particles like Very Low & Intermediate Density cholesterol, are being

overlooked, by targeting mainly the Low Density cholesterol. Hence , Adult Treatment Panel III generated the idea of non-HDL cholesterol. This includes all the dangerous atheroma-prone lipoprotein subdivisions. Non-High Density Cholesterol target is 30mgs% more than the LDL levels. This has to be used when TGL level is more than 200 mgs%.

In such persons who fail to reach the desired targets, with intensive lifestyle interventions, pharmacological treatment with statins has to be started. Lipid lowering drugs decreased unwanted cardiovascular events and CVAs in many clinical trials. The lipid lowering therapy, had additional beneficial effects in diabetes patients. This has been documented in Collaborative Atorvastatin Diabetes Study &
Heart Protection Study. This has been proven, even when the cholesterol is within normal limits. Statins decrease all the apoB– lipoproteins . they successfully reach Adult Treatment Panel III targets for the Low Density & non-High Density cholesterol in persons having MetS.

Fibric acid congeners modify majority of the components of the atherogenic lipid consitution in MetS. This improves mainly the decreased HDL , elevated TGLs and small, dense LDL particles. Their use has to be thought of in all persons with a risk of more than 20% for CAD. Nicotinic acid at higher dosage, also modifies HDL & TGL levels, with the comparable efficiency to fibrates. On the downside, nicotinic acid causes impaired glucose tolerance & elevates serum uric acid levels. Hence, this can not be used in persons with MetS.

Procoagulant & proinflammatory condition:

In MetS, inflammatory mediators such as , Interleukin-6 and Tumor Necrosis Factor– α and acute phase proteins like, C-Reactive protein and fibrinogen are elevated. PAI-1 levels are mainly increased. Tissue plasminogen activator activity is

decreased. This contributes to the characteristic inflammatory-prone & procoagulant environment of the MetS.

The therapeutic and prognostic role measuring inflammatory mediators is doubtful. This is an upcoming area of scope in preventive cardiology. Eventhough assessment of fibrinogen & procoagulation factors is not routinely advised. AHA current recommendation is for anti-platelet prophylaxis in persons with a more than 10% risk for CAD.

SUB-CLINICAL HYPOTHYROIDISM

Definition:

SCH is **defined** as a serum **thyroid**-stimulating hormone (TSH) level above the upper limit of normal despite normal levels of serum free thyroxine. TSH levels 5.5–10.0 Mu/l correspond to prevalence of SCH.

The incidence of subclinical hypothyroidism ranges from 6 to 8% , based upon the sex , age and ethnicity of the subjects studied. The effects of subclinical hypothyroidism depends upon the duration and the degree of thyroid dysfunction as measured by TSH.

Table 3

Recommendations Regarding Screening of Asymptomatic Adults For Thyroid Dysfunction

Organization	Recommendations
American Thyroid Association	Women and men ages >35 should be screened every 5 years
American Association of Clinical Endocrinologists	Older patients, especially women, should be screened
American Academy of Family Physicians	Patients ages ≥60 should be screened
American College of Physicians	Women ages >50 with an incidental finding suggestive of symptomatic thyroid disease should be screened
U.S. Preventive Services Task Force	Insufficient evidence for or against screening
American College of Obstetrics and Gynecology	Women in "high-risk" groups (those with autoimmune disease or a strong family history of thyroid disease) should be screened starting at age 19

Effects of Thyroid Hormones on Lipid Metabolism:

Thyroid hormones play an influential role in most of the steps of lipid metabolism including production, transport and storage. Thyroxine promotes the cholesterol production by

potentiating the action of HMG co-A reductase, present in the hepatic parenchyma.

Thyroxine induces the action of LPL. Thus results in increased hydrolysis of TGLs into VLDL. Also the chylomicrons are hydrolysed as free fatty acids & glycerol. In thyroxine deficiency, the LPL action level over the fatty tissue is documented to be either normal or suppressed. In the mean time, hepatic lipase action is also suppressed, causing elevated measures of TGLs.

Thyroxine levels also directly affect the CETP levels and action. Reduced thyroxine, decreases CETP activity. As a result both total & subfraction of HDL levels are markedly decreased. Biologically active form, T3, stimulates reseptor gene expressivity. This results in augmented clearance of Low Density Cholesterol. Also the T3, increases 7-alpha hydroxylase activity. All these cumulatively explain the decreased Low density

cholestrol clearance and hence, increased serum low density cholesterol levels in SCH.

Lipid metabolic disturbances in SCH:

Hyperlipidemia is a very common laboratory abnormality in persons with evidence of hypothyroidism, including elevated levels of both total & Low density cholesterol. Researches pertaining to TGLs, Lp(a), HDL, apoB & apoA1 components in subclinical hypothyroidism are minimal. In addition to the quantitative changes, qualitatives changes like, smaller, denser and more oxidized Low density cholestrol is a routine feature of hypothyroidism.

Both qualitative and quantitative changes in total & Low density cholesterol are directly linked to measure of thyroid levels in SCH. After thyroxine replacement therapy, there occurs a significant improvement in these abnormalities. But TGLs, apoB, apoA1, Lipoprotein-a levels, may or may not be adequately

controlled after therapy. This suggests a highly perplexed etiology for lipid abnormalities in SCH.

Not only overt hypoT, but also the SCH is also linked to profound lipid composition. The changes include the elevated total & low density cholesterol. Whereas HDL, TGLs, apoB, Lp-a & apoA1 levels did not show marked changes subclinical hypothyroidism when compared to the euthyroid controls , in most of the observations. Rondeau et al. noticed a negative correlation between HDL-C and TSH levels in obese and postmenopausal females.

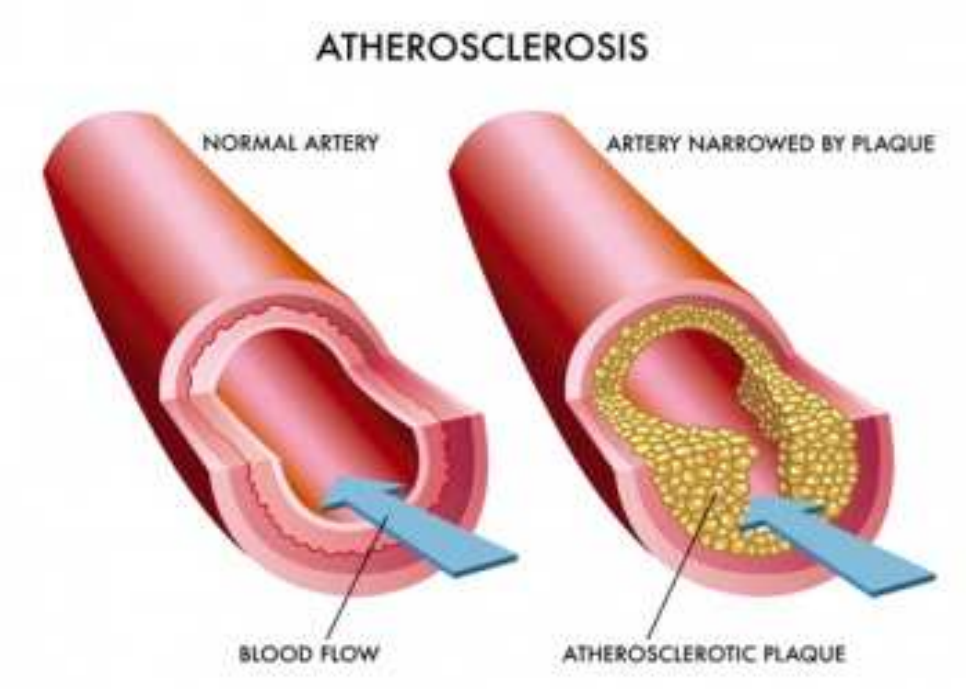
Most of the researches have found that after thyroxine replacement treatment, both the total & Low density cholesterol levels are being normalized . Whereas hormone replacement studies in SCH, have shown that the therapy has only a limited influence over the serum levels of TGLs, apoA1, HDL, apoB & Lp-a. Reduced transfer of TGLs to high density cholestrol

& phospholipids in SCH was corrected after achieing euthyroid status.

Hemodynamic effects of thyroid dysfunction:

In overt hypoT, the prime modifications of cardiovascular functions, noticed are reduction in heart rate, increased peripheral vascular impedance, elevated diastolic blood pressure & hence, the afterload. Also there occurs reduced blood volume & hence, the preload. Put together, cardiac output is diminished. During exercise, left ventricular systolic contractility is impaired. Also, the LV diastolic relaxation is reduced during both rest & exercise. These changes occur both in the overt & subclinical hypoT. In elderly, hypoT is associated with diastolic dysfunction of the heart.

Thyroid Dysfunction & Atherosclerosis:



Thyroid dysfunction is associated with the highly atherogenic dyslipidemia. In addition, insulin insensitivity, hypertension, inflammation, oxidation stress & coagulation abnormalities are enhanced by thyroid dysfunction. These factors prove that a multitude of risk factors for atheroma formation, in thyroid dysfunction, dyslipidemia playing a major part.

Clinical hypoT is related to elevated diastolic blood pressure and hyperhomocysteinemia. Increased levels of hs-CRP and coagulation deficits have also been reported in patients with hypothyroidism. The proposed mechanisms being, impairment of intracellular glucose metabolism & translocation GLUT4. Enhancement of carotid artery intimal thickness, is also being noticed in persons with both clinical/subclinical hypoT.

In a survey conducted in Whickham , a positive correlation has been documented between the incidence of CAD and associated mortality in persons with SCH, followed over a period of two decades. This positive correlation was abolished after thyroxine replacement therapy .

Extending support to this observation, many meta-analyses suggest that SCH is related to a marked rise in risk of CAD & associated mortality. In a meta-analysis done by Razvi et al., in patients younger than 65 years old , the incident rate of CAD and associated mortality, found to be elevated in

persons with SCH. This is more true in case of women. SCH is also causally, linked with the incidence of cerebral ischemia. Rodondi et al. noticed a correlation between SCH & the risk of ischaemic stroke.

SCH and CV Disease Risk:

The CV modifications observed in SCH patients qualitatively resemble those produced by overt hypothyroidism, quantitatively, to a lesser extent. Early alterations of cardiac performance, endothelial function, systemic blood pressure, and lipid profile have been documented in SCH patients. This supports a biologically plausible role for subclinical hypothyroidism in the development of early atherosclerosis.

Serum lipid abnormality is prevalent in sub-clinical hypothyroidism, and it is considered to cause

cardiovascular disorders. Furthermore, it has been reported that SCH is associated with high serum total cholesterol and LDL levels and low HDL which could increase the atherosclerosis risk.

A significant correlation between SCH & CAD morbidity and death has been documented , although less evident in older people. The relationship between SCH and CHD persisted even after adjustment for traditional risk factors. This suggests an alternative mechanism by which SCH increases CV risk, at least in younger individuals.

Although the scientific literature is not uniform in the definition of the effect of SCH with mild TSH elevation (<10 Mu/L) in terms of CV events and mortality, available data suggest an impact of this clinical condition only in younger patients (<65 y), especially men.

In another study on SCH and its cardiac impacts, diastolic cardiac dysfunction in the resting period and systolic dysfunction in the exercise period and a reduced exercise capacity were reported.

Treatment guideline for SCH:

In most of the patients with subclinical hypo-T, there is no need for treatment. Oral Levo thyroxine is the drug of preference, in case of a decision to treat the deficiency. Clinical trials of subclinical hypo-T patients, have proven that thyroxine therapy is effecient in reducing TSH to the normal reference range.

Ideally, thyroxine has to be started at a dose of 25-50 μg od. Followed up with a monthly dosage adjustment to achieve the desired TSH value. In a study, 100 elderly persons >65yrs of age, achieved the desired TSH level, with a replacement dose of 50μg of thyroxine . In two more RCTs, done in young subclinical hypo-T persons , it has been proven that on an average, thyroxine at a dose of 50-75 μg is needed to bring TSH level into the normal.

In an another study, involving 35 subclinical hypo-T persons , it has been that, on an average 100 μg of thyroxine, is needed to maintain TSH levels between 0.5 - 2.5 Mu. In a large clinical study, all subclinical hypoT patients, when started on 100 μg thyroxine od, discovered that only 10% developed features of hyperthyroid as evidenced by low serum TSH and increased T 4 levels . Henceforth, the thyroxine dosage of 50 – 100 μg od is sufficient to bring down TSH, to desired levels in most of the persons.

In many situations, the patient has to be started on the approximate full dose of thyroxine . The exception being, known patients with coronary arteriak heart disease. In such patients, much lower doses have to be started, followed by gradual stepwise dose escalation. For example, in a patient with stable angina, thyroxine has to be started & increased slowly by 25 μg once in 2- 3 weeks. Eventhough a quiet identitical approach is undertaken in elder persons, especially >70 yrs of age, a RCT

has shown that such a cautious approach is not needed in elder population , without any cardiac disease.

For maximal bioavailability, thyroxine has to be consumed on an empty stomach. Studies have given varied results with regard to the ideal time for thyroxine replacement therapy. A study conducted in United States population, showed adequate TSH control, if thyroxine is consumed on an empty stomach state, one hour before food . But in a Denmark study, thyroxine consumed just before bedtime is higher in efficacy, when compared to that consumed one hour before breakfast.

There are many drug-food interactions. Milk, coffee, soya & papaya especially hamper thyroxine absorption. In reality, a lot of medications including
Salts of calcium & iron, antacids such as sucralfate,
H 2 blockers & PPIs, result in significant interference to absorption of thyroxine .

Likewise, a lot of GI conditions tend to negatively impact on absorption of thyroxine. Some of such conditions are

atrophic gastritis, celiac sprue & pernicious anaemia. Both impairment & improvement of thyroxine absorption are documented following various types of bariatric surgery . Patients falling in these situations tend to need increased dosage of thyroxine.

There is a possible theoretical advantage by combining T 3 &T4 medication. But so far, studies using Combination of T 3&T4 medications did not document any definite advantage in patients with clinical hypoT.

Also, in a meta-analysis of studies involving more than 1,500 hypoT persons, no convincing advantage of T 3&T4 combination was found. In this setting, without any data pertaining to subclinical hypo-T , this combination therapy should not be prescribed in routine practice for them.

After starting replacement therapy with thyroxine, patients have to undergo follow-up after 6–10 weeks. With the repeat TSH value, thyroxine dose altered accordingly. This is to make sure that TSH falls into the desired range. In patients who all have, dyslipidaemia ie before starting therapy with thyroxine ,

the serum lipid profile has to be re-evaluated. This follow-up, is to assess sufficient improvement or is there any need of pharmacological therapy for dyslipidaemia. In the mean time, re-evaluation of symptoms of hypoT, in patients with subclinical hypo-t , who were commenced on thyroxine replacement for possible symptoms of hypoT. This is very important, because if at all any benefit from thyroxine replacement in subclinical hypo-T, then it is worthwhile in considering prolonging treatment for lifelong. If following a three-six months of therapeutic trial, there has not been any significant symptomatic improvement, then it is time to consider stopping replacement therapy.

A significant number of persons with subclinical hypo-T will develop clinical hypoT. This progression has been found to be around 6–10% per annum, degree of TSH elevation being the important predictor . On the other side, sub-normal thyroid production may normalize in 8–30% of subclinical hypo-T. This normalization depends upon baseline TSH values, autoantibody against thyroid and duration & frequency of follow-

up. As a result, in most of the patients, thyroid function seems to be stable.

If a patient is diagnosed with SCH, then the thyroid function has to be re-evaluated after a period of 2-3 months, in addition to thyroid autoantibodies. If there is normalization of thyroid secretion, no more testing is needed in asymptomatic patients without either thyroid autoantibodies or goitre.

In patients with persistent subclinical hypo-T, thyroid function has to be re-evaluated , once in six months, at least for the first two years & thereafter once a year only. This Will assess any tendency to progress & to identify consequent clinically evident hypoT.

Objectives of Study:

a) To find out the type of thyroid dysfunction in metabolic syndrome.

b) To find out the association of thyroid dysfunction with the components of metabolic syndrome.

MATERIALS AND METHODS:

Source of Data

Patients attending OPD of Dept of Internal Medicine, Tirunelveli Medical College Hospital, who are being diagnosed as metabolic syndrome and fulfill inclusion and exclusion criteria.

Method Of Collection of Data

Sample size:

100 subjects with MetS & 50 controls.

Sampling Method : Simple random sampling

Inclusion Criteria:

Patients fulfilling the criteria for metabolic syndrome by International diabetic foundation[IDF] were taken into study.

Patients with metabolic syndrome not on any medications – newly detected metabolic syndrome patients.

Exclusion Criteria:

1) Known patients of hypothyroid or sub-clinical hypothyroid or hyperthyroidism

2) Patients on medications for diabetes mellitus , hypertension , thyroid disorders and dyslipidemia

3) Patients on steroids

4) Acutely ill patients

5) Individuals less than 18 years age, who can not give consent.

Method of study:

The purpose of the study was explained to the patient and informed consent was obtained. Data was collected using a pretested proforma meeting the objectives of the study. Detailed history and necessary investigations were undertaken. Patients were selected for study who satisfied all the inclusion and exclusion criteria. Patients were diagnosed having metabolic syndrome by the,

"IDF criteria:

Central obesity – defined as waist circumference with ethnicity specific values (for south Asians : ≥90 cm for Men and ≥80cm for women were used)

AND any two of the following:

- Raised triglycerides: > 150 mg/Dl (1.7 mmol/L), or specific treatment for this lipid abnormality.
- Reduced HDL cholesterol: < 40 mg/Dl in males, < 50 mg/dl in females, or specific treatment for this lipid abnormality

- Raised blood pressure: systolic BP > 130 (or) diastolic BP >85 mm Hg, or on treatment for previously diagnosed hypertension.
- Raised fasting plasma glucose ☹FPG)>100 mg/dl , or previously diagnosed type 2 diabetes mellitus"

All the patients enrolled for the study, were subjected to Thyroid Function Test. Test results were entered in a excel sheet. Meticulous analysis of the data was carried out.

INVESTIGATIONS

1. Fasting blood sugar
2. Lipid profile includes Triglycerides , HDL ,LDL, Total cholesterol
3. Thyroid assay includes T_3 , T_4 , TSH
4. Blood pressure recording
5. Height , weight , waist circumference

RESULTS AND OBSERVATION

Statistical method:

All the compiled data were analysed using computer based software. By chi-square test p-value was calculated.

P-value < 0.05 was considered as statistically significant.

Age distribution among the subjects:

	Men			Women		
	<30yrs	30-40yrs	>40yrs	<30yrs	30-40yrs	>40yrs
MetS	3	27	9	8	38	15
Control	5	13	7	5	18	2

The mean age of the MetS subjects was around 36 years. The mean age of the controls was found to be 34.7 years. This difference had no statistical significance. This implied that the subjects and the controls were comparable, with respect to their

age. Thus the impact of age, on the incidence of SCH, was negated, in the study population.

As clearly seen from the above chart, more than two-thirds of the subjects fall in the 30-40yrs age category. Clustering of MetS in the 30-40yrs age group, reveal the deleterious effects of the wrong life-style patterns in the past two decades.

The important thing to be considered is, this 30-40yrs population, is the backbone of a growing economy like ours. Hence, any health related issue, affecting this population, will produce a significant negative impact on the nation's development.

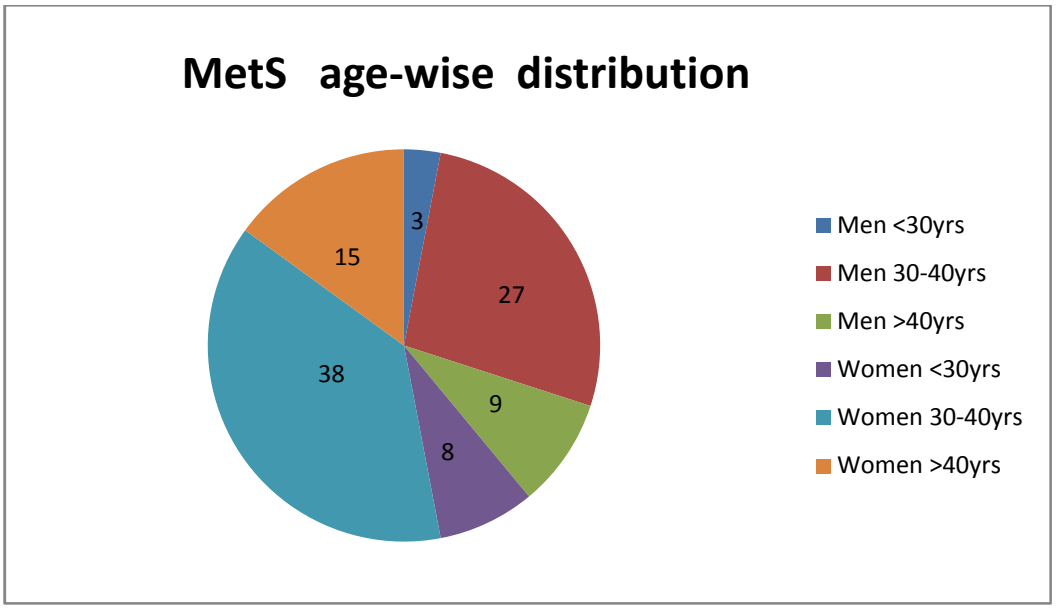


Figure 1

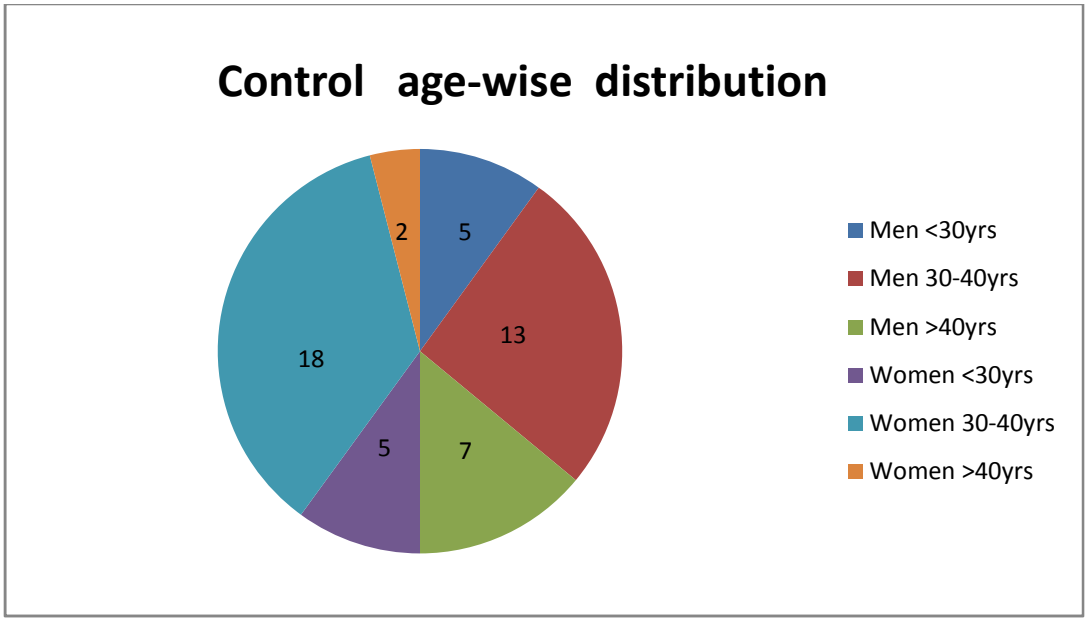


Figure 2

Sex distribution of MetS subjects:

Met S in men	39
Met S in women	61

Out of the 100 MetS subjects, 39 were male and 61 were female. This is consistent with the results of many observational studies, which found out that the incidence of metabolic syndrome is 1.5-2 times higher in females compared to males.

p-value <0.05, this means, the sex difference noted in the prevalence of MetS is statistically significant.

The female sex, supposed to have protective effect against, CV diseases, is the easy target for MetS. This strong

clustering of CV risk factors, negates the natural protection for women, against cardiovascular diseases.

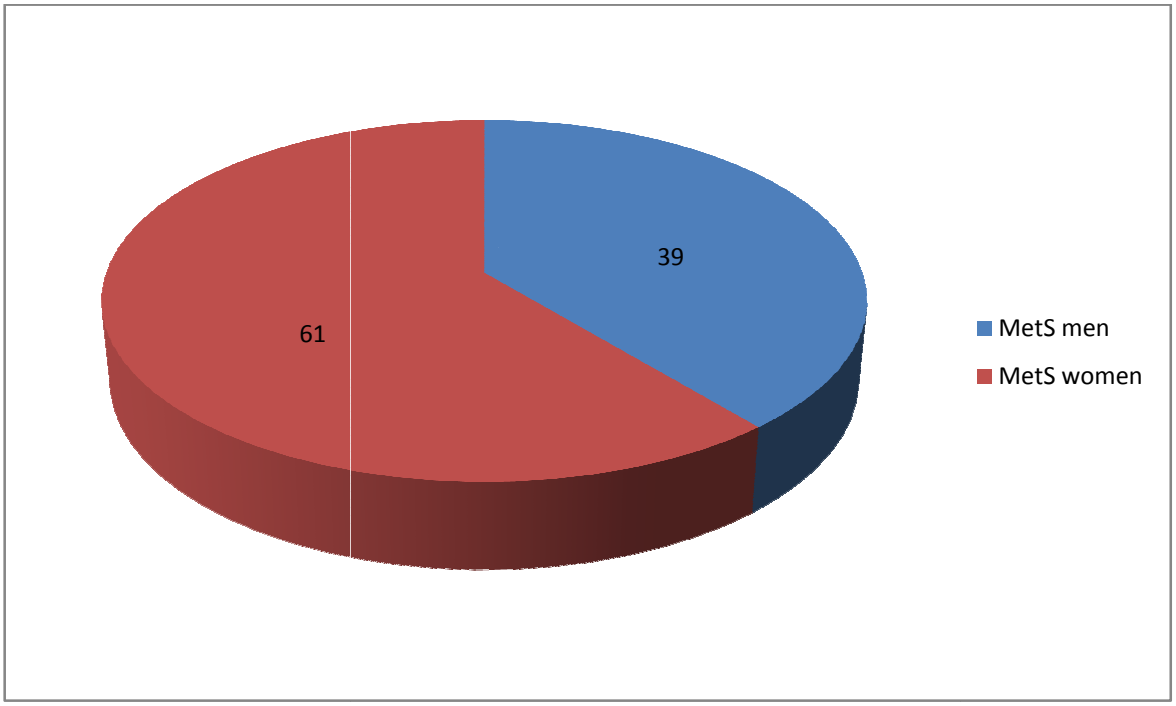


Figure 3

The popular belief that premenopausal women have immunity against CV diseases, is becoming a thing of past. If not taken seriously, this will haunt the future, of fertile female population. This MetS, being associated with PCOS, will leave a question mark over their fertility itself.

Prevalence of SCH in MetS:

Control with TSH<5.5	47
Control with TSH>5.5	3
Mets with TSH<5.5	79
Mets with TSH>5.5	21

Of the 100 MetS subjects, 21% had sub-clinical hypothyroidism. Of the 50 controls, only 3 had SCH, which means the prevalence among the control population is around 6% only.

p-value <0.05, this means, the difference in prevalence of SCH in MetS & controls is statistically significant.

Both SCH and MetS, individually being CV risk factors, their combination more than doubles the risk. This being the era of non-communicable diseases, these two are the most easily treatable potential risk factors, in the prevention of cardiovascular diseases.

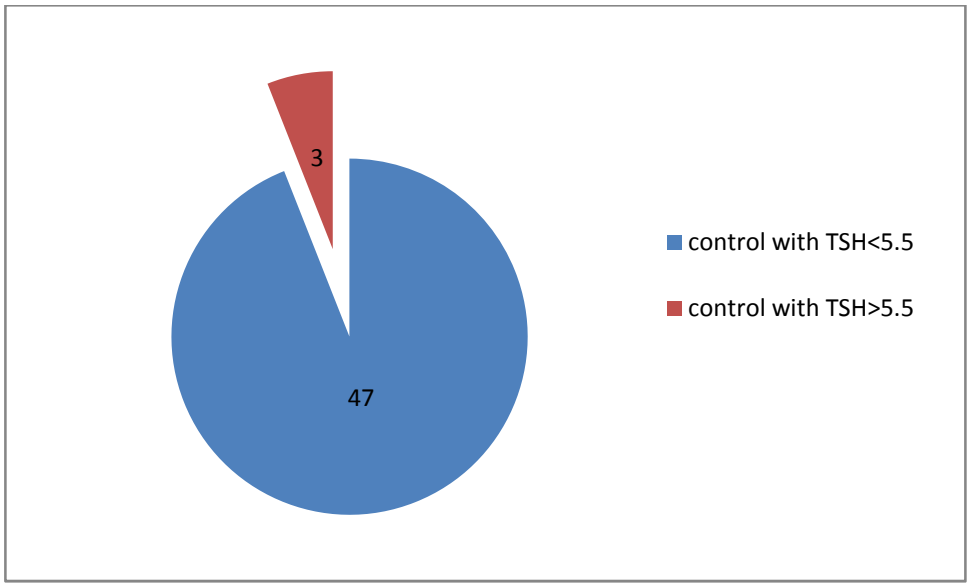


Figure 4

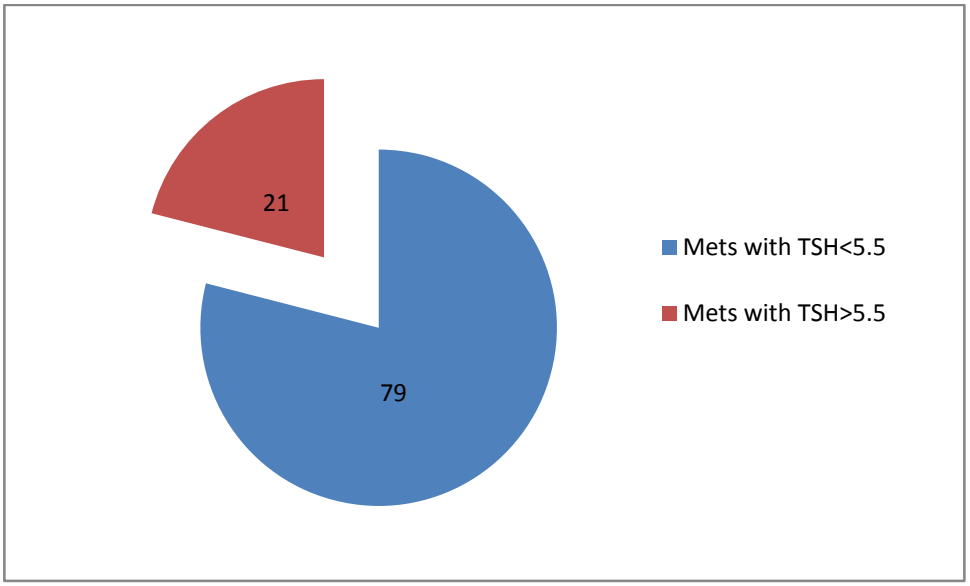


Figure 5

Sex-wise prevalence of SCH:

	Men	Women
SCH in MetS	4	17
SCH in control	1	2

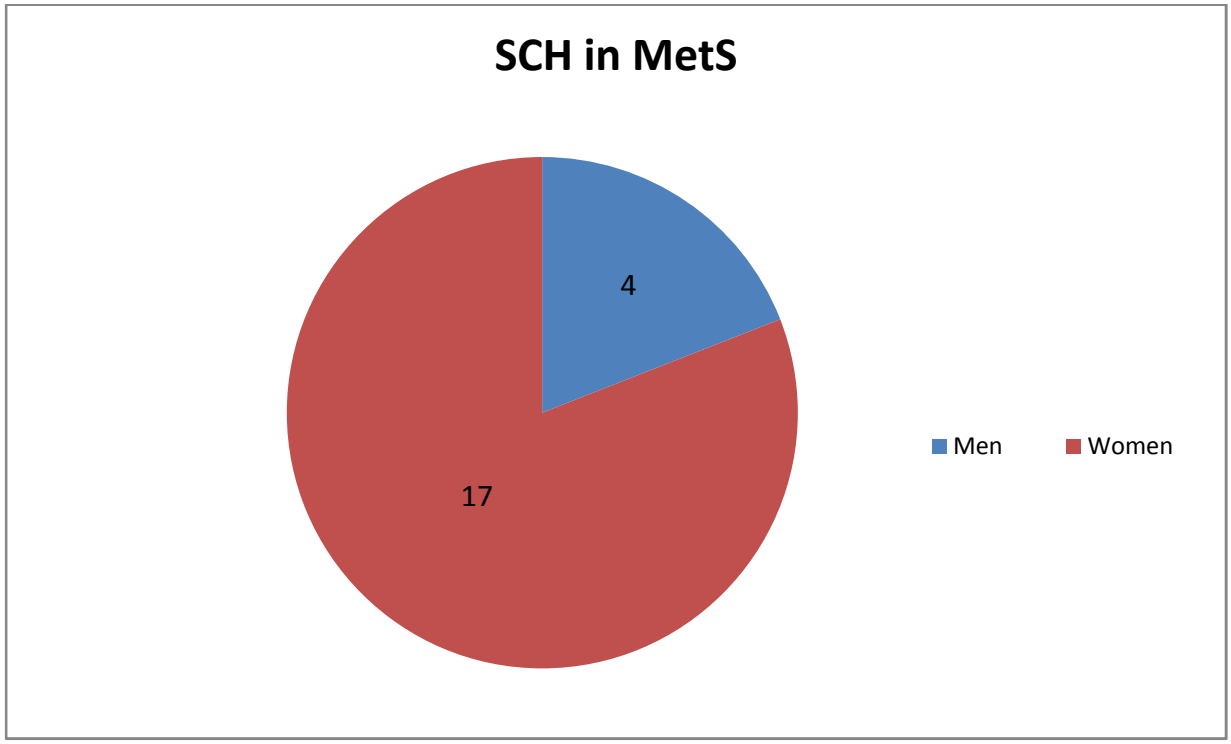


Figure 6

More than 80% of the MetS with SCH were women. p-value < 0.05, statistically significant.

BMI-wise distribution of Thyroid function:

	avg BMI
MetS with SCH	26.7
MetS with euthyroid	25.9
Control	21.4

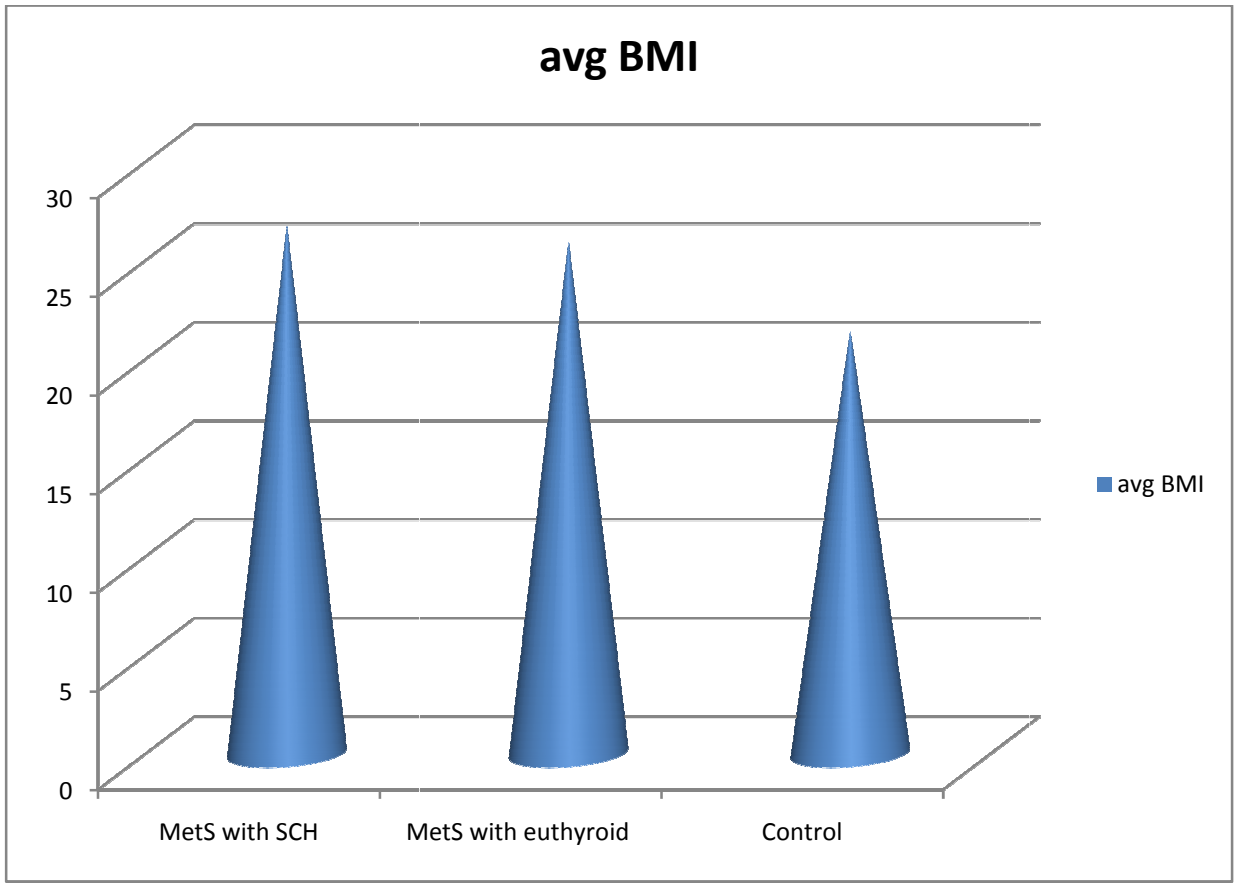


Figure 7

BMI was calculated using the formula,

BMI=weight in kg/ height in m^2 .

As expected, BMI was significantly higher in MetS, compared to the controls. But the difference was not significant, among MetS with SCH & MetS with euthyroid status. P-value >0.05, implying, no statistical significance.

This reiterates the "**thin fat asian phenotype**" concept. BMI is not an ideal marker, in asian population, when compared to their european counterparts.

Visceral adiposity, is the determining factor, in the definition of metabolic syndrome. The indian urban population don't indulge in regular physical activities. So, their muscle mass & bone mass are on the lower side. This the reason for their lower BMI, despite of their look being fatty.

Comparing thyroid function with MetS components:

Waist circumference:

	Men WC (cm)	Women WC(cm)
MetS with SCH	100.3	93.6
MetS with euthyroid	95.5	87.5

Waist circumference is the essential criteria for diagnosing metabolic syndrome. Both men and women with MetS, have higher WC, compared to their euthyroid counter-parts. But, this difference is subtle, with a p-value>0.05, statistically insignificant.

Waist circumference is the indirect measure of visceral adiposity. This has been also found to be associated with the incidence of, fatty liver and NAFLD.

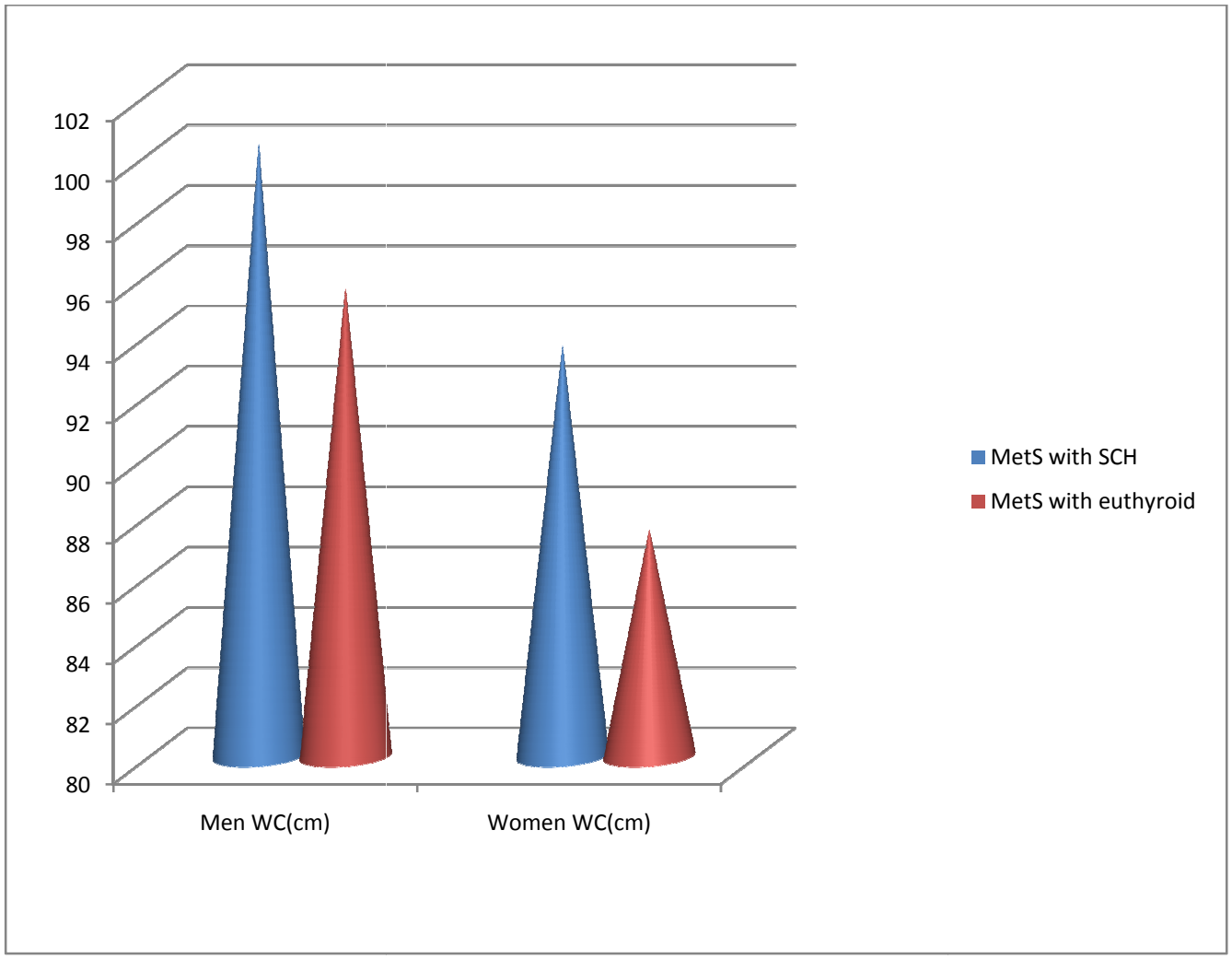


Figure 8

Though there is a significant arithmetic difference in the waist circumference between both the groups, the p-value is >0.05, conferring no statistical significance.

Thyroid function vs FBS:

	Men FBS(mgs%)	Women FBS(mgs%)
MetS with SCH	101	99.5
MetS with euthyroid	95.5	98.7

Fasting blood sugar, among MetS, was in the range of 88-115mgs%, with the average value being 97.7mgs%. Out of the 18 women with both MetS & SCH, 8 had a FBS value more than 100mgs%. Out of the 3 men with both MetS & SCH, 2 had a FBS value more than 100mgs%.

The difference between the average FBS, between the MetS with SCH and MetS with euthyroidism is only marginal.

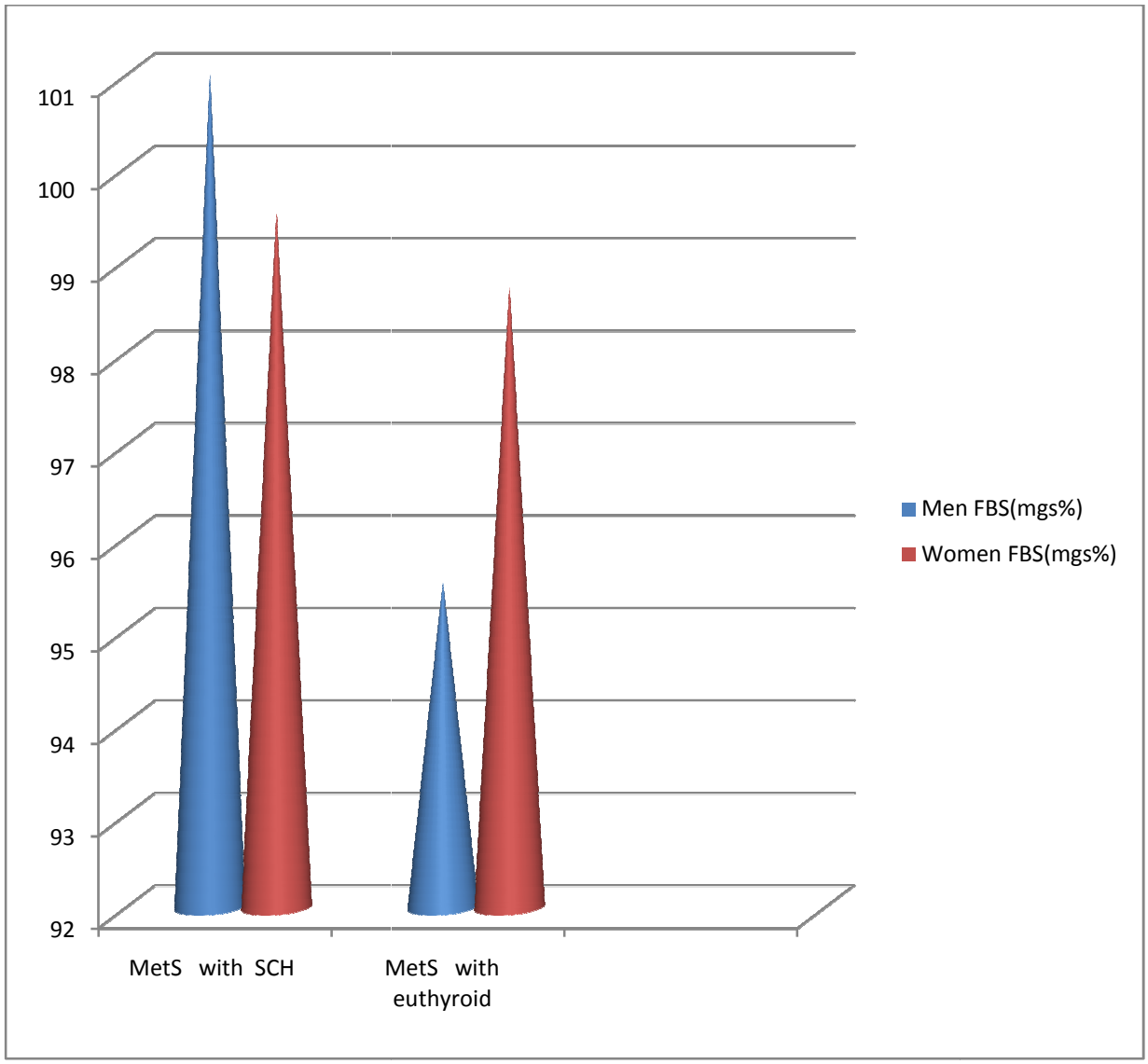


figure 9

This difference in FBS, had no statistical significance, as the p-value was >0.05.

Thyroid function vs TGL:

	Men TGL(mgs%)	Women TGL(mgs%)
MetS with SCH	182.3	182.2
MetS with euthyroid	139.5	141.2

Fasting Triglycerides, among MetS, was in the range of 112-230mgs%, with the average value being 148.7mgs%. Out of the 18 women with both MetS & SCH, all 18 had a TGL value more than 150mgs%. Out of the 3 men with both MetS & SCH, all 3 had a TGL value more than 150mgs%. This strongly implies that raised TGL, is an integral aspect of patients with both MetS & SCH.

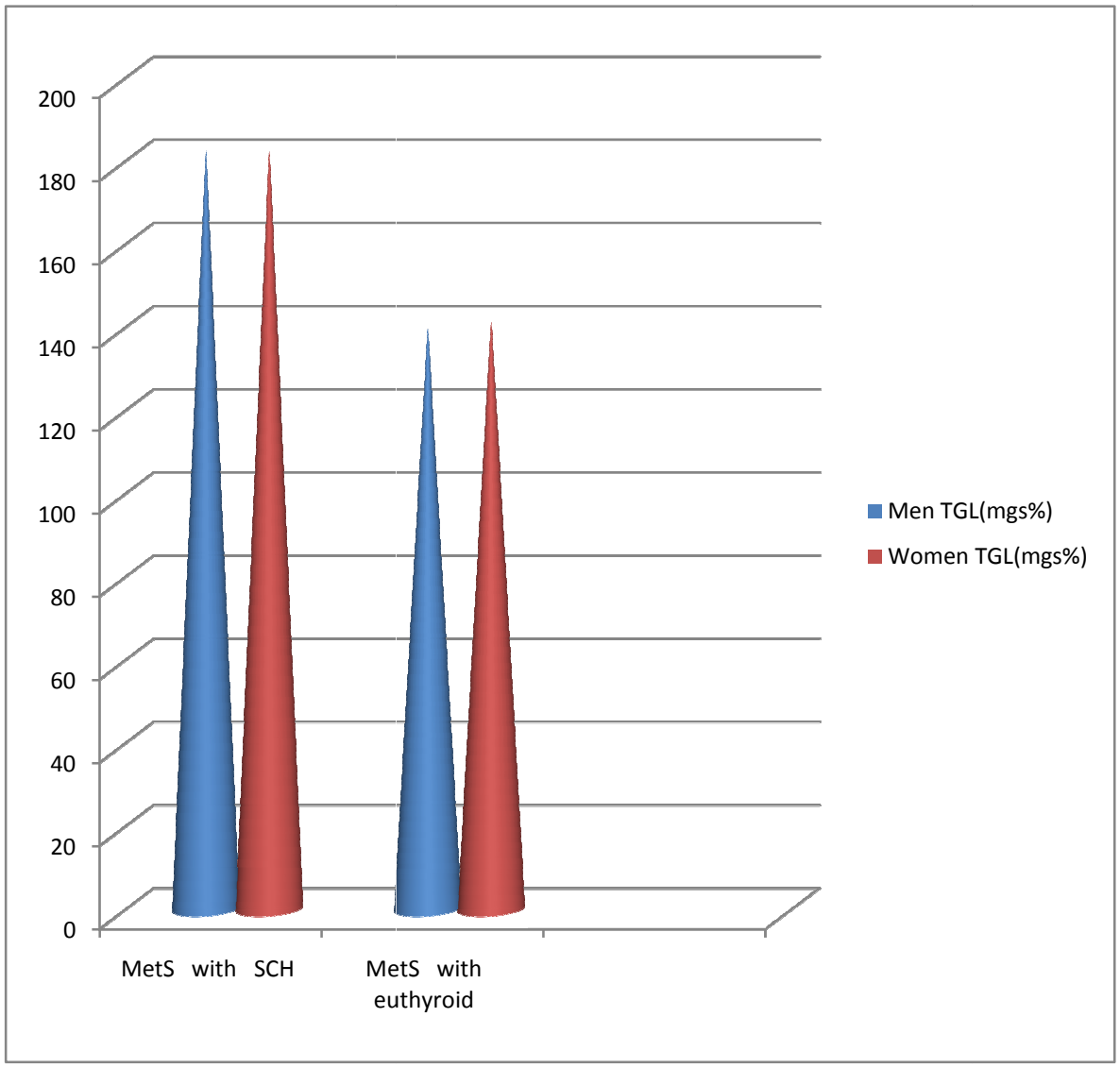


Figure 10

This significant difference in TGL values, among the groups is authenticated by the p-value <0.05. Hence raised TGL value, more than 150mgs%, in MetS should evoke suspicion to screen for thyroid dysfunction.

Thyroid function vs HDL:

	Men HDL(mgs%)	Women HDL(mgs%)
MetS with SCH	37	45.6
MetS with euthyroid	36.2	46.5

Out of the 18 women with both MetS & SCH, 14 had a HDL value less than 50mgs%. Out of the 3 men with both MetS & SCH, 2 had a HDL value less than 40mgs%.

When compared to their, euthyroid counterparts, both men and women with MetS & SCH, had similar HDL values. This rules out HDL, being a definite marker to screen for thyroid dysfunction among MetS subjects.

This also stresses the fact that, in MetS, non-HDL control is more important than improving HDL values alone.

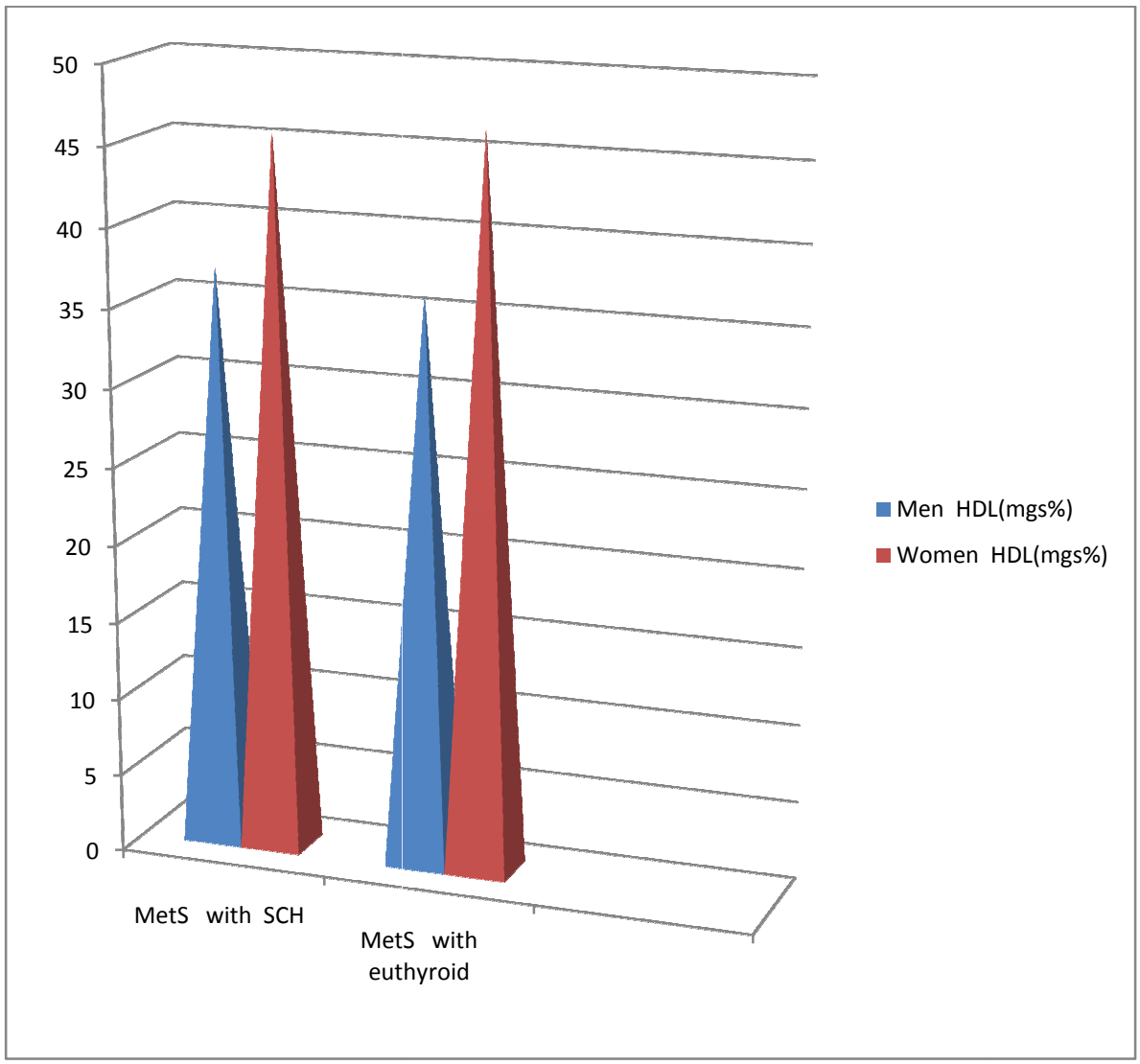


Figure 11

Almost similar HDL values, among the groups, leaves this criteria being insignificant, with the p-value >0.05.

Thyroid function vs SBP:

	Men SBP(mm Hg)	Women SBP(mm Hg)
MetS with SCH	132.7	129.9
MetS with euthyroid	136.6	131.4

Out of the 18 women with both MetS & SCH, 7 had a SBP value more than 130mm of Hg. Out of the 3 men with both MetS & SCH, 1 had SBP value more than 130mm of Hg.

When compared to their, euthyroid counterparts, both men and women with MetS & SCH, had similar SBP values. This rules out SBP, being a definite marker to screen for thyroid dysfunction among MetS subjects.

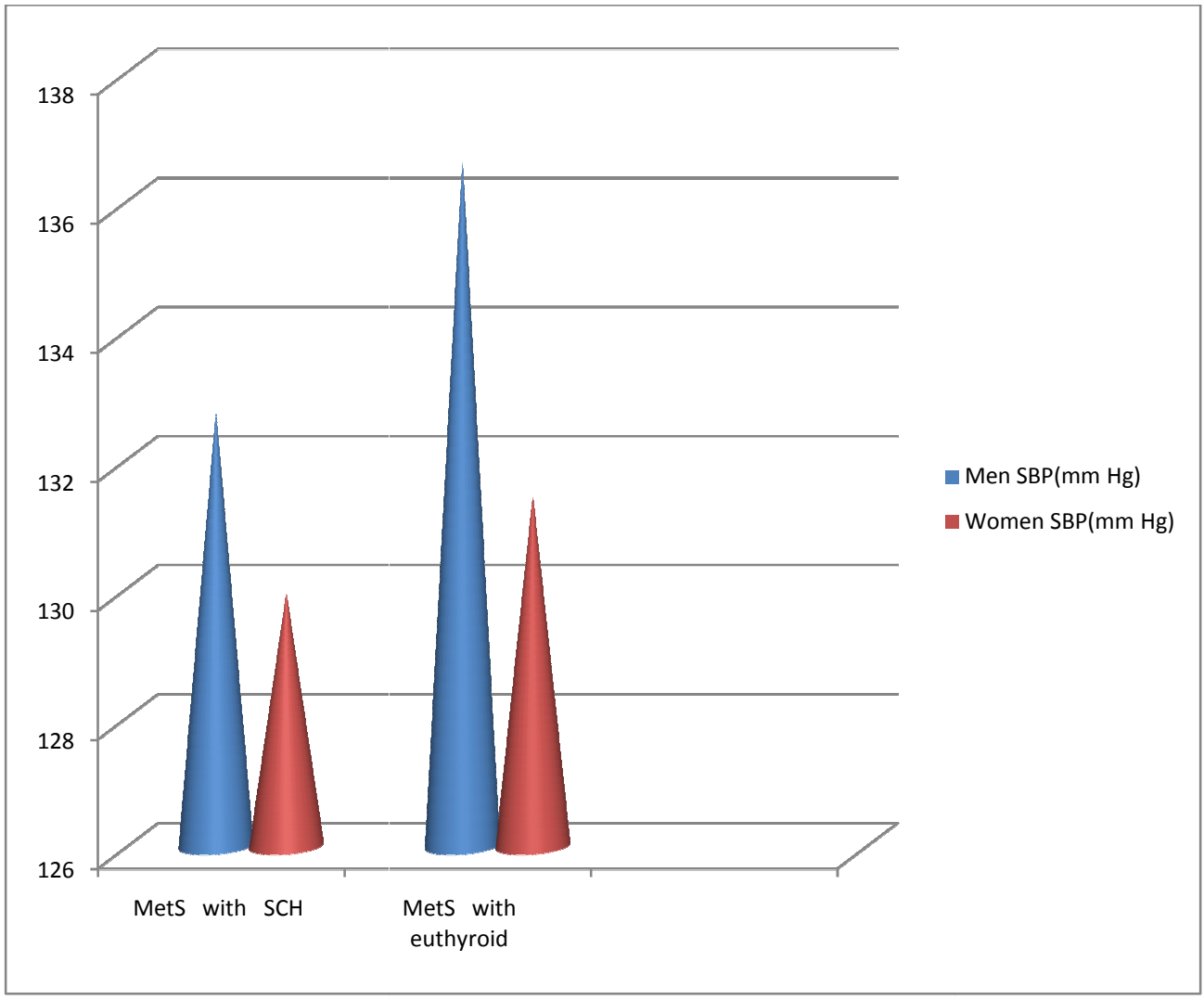


Figure 12

In SCH, the heart rate and the stroke volume are decreased. This results in a fall in SBP in cimparison to MetS with euthyroidism. As a result, for the difference in SBP, among the groups, p-value is >0.05, statistically insignificant.

Thyroid function vs DBP:

	Men DBP(mm Hg)	Women DBP(mm Hg)
MetS with SCH	88	84.5
MetS with euthyroid	88.5	85.7

Out of the 18 women with both MetS & SCH, 9 had a DBP value more than 85mm of Hg. Out of the 3 men with both MetS & SCH, 1 had DBP value more than 85mm of Hg.

The increase in DBP is due to increased arterial stiffness in both MetS and SCH. But when compared to their, euthyroid counterparts, both men and women with MetS & SCH, had similar DBP values. This rules out SBP, being a definite marker to screen for thyroid dysfunction among MetS subjects.

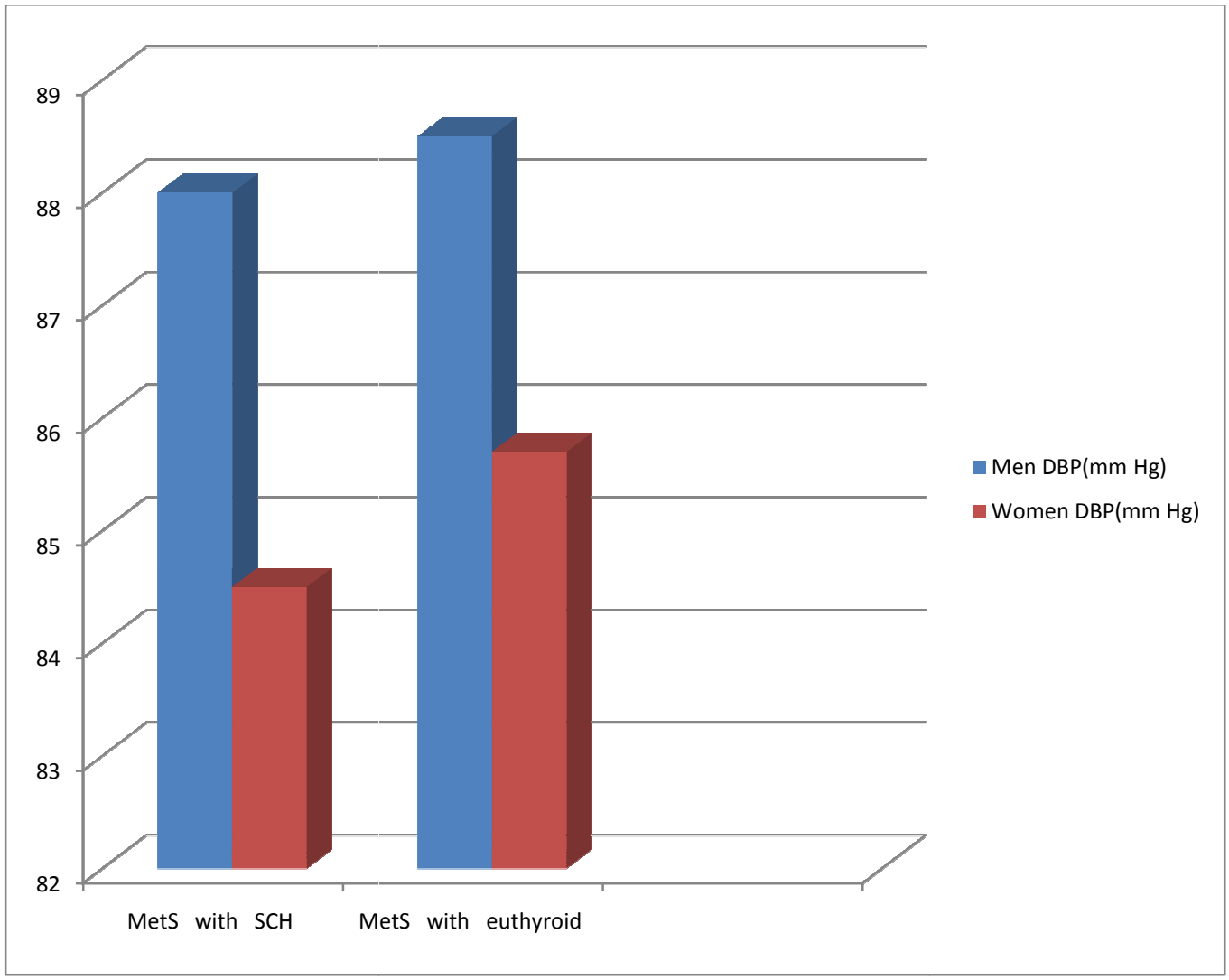


Figure 13

Almost similar DBP values, among the MetS with SCH & those with euthyroidism, leaves the p-value >0.05, ie, the association is statistically insignificant.

DISCUSSION:

In our study, of 100 MetS, majority were in the 30-40yrs age group, highlighting the at-risk population. Fast changing food habits and sedentary life style pattern, in the last two decades, could be the answer for this metabolic abnormality. This means, economic backbone of our country, is amidst a crisis regarding to health issues.

The prevalence of MetS in women is more than two times, compared to men, in this study. The prevalence of SCH in MetS, was found to be 21%, when compared to only 6% in the control population. This association with SCH, is more frequent among women. Due to increasing sedentary life style changes, the natural immunity against cardiovascular diseases for the women, is at risk.

The thyroid dysfunction in MetS, is statistically significantly associated with the serum triglycerides, followed closely by the waist circumference. This association is not found with the other components of MetS.

The almost nil difference among the subjects, in regard to HDL, once again reiterates the fact that non-HDL cholesterol has to be closely monitored.

Unless, strictly managed this double whammy of SCH and MetS will result in a heavy toll, in our growing economy. Intensive life-style, has to be initiated in a much younger population, ie school going children. Only this primordial intervention, can produce significant changes, helping to avert this middle-age menace.

Conclusion:

Due to the alarming rise, in CV mortality and morbidity, the people at risk have to be identified at the earliest and their risk factors modified. Hence, **diagnosing MetS should become a routine practice** among the medical fraternity.

Even if routine screening for SCH among MetS is not feasible among all patients, **Screening for thyroid dysfunction, in MetS, especially those with elevated triglycerides,** has to become a part of treatment.

Patients diagnosed to have a double jeopardy, of **MetS with SCH, should be intensively treated**, with life-style Interventions and if needed, with pharmacological therapy, **to achieve the desired therapeutic targets.**

Limitations:

There are few limitations of the present study, first is, this **being a cross-sectional study, a cause and effect relationship could not be determined**. Further large scale cohort study is needed to evaluate the deleterious effect of subclinical hypothyroidism on cardiovascular disease and metabolic functions.

. Second, this study did not find the association between TSH and many components of MetS , the reason might be there were **only few subjects with subclinical hypothyroidism**. Therefore, large epidemiological studies are needed to evaluate the relationship between SCH in patients with MetS.

Though T3 and T4 values are within normal limits with isolated TSH elevation, without significant symptoms, the diagnosis of SCH was made, in this study. But, **FT4 was not measured** due to non-feasibility.

Scope for future study:

The reason for subclinical hypothyroidism, among MetS, could be cytokine mediated injury. MetS is a well known pro-inflammatory state, causing excess release of interleukins and interferons.

This augmented cytokine release may mediate injury to thyroid follicles, exposing the enzymes on the apical border of follicles to TPO antibodies which may then bind to autoantigens and fix the complement leading to hypothyroidism. This proposed mechanism, has to be scientifically studied, by comparing these inflammatory markers against TSH and TPO antibody.

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ABBREVIATION

MetS --- metabolic syndrome

SCH --- subclinical hypothyroidism

WC --- waist circumference

FBS --- Fasting blood sugar

HDL --- high density lipoprotein

TGL --- triglyceride

LDL --- low density lipoprotein

VLDL --- very low density lipoprotein

SBP --- systolic blood pressure

DBP --- diastolic blood pressure

CVD --- cardiovascular diseases

CRP --- C-reactive protein

TSH --- thyroid stimulating hormone

apoA --- apolipoprotein A

apoB --- apolipoprotein B

Lp-a --- lipoprotein a

PAI --- plasminogen activator inhibitor

PROFORMA

Name :

Age :

Sex :

Height :

Weight :

BMI :

BP :

Waist circumference :

Medical history :

Current medications :

Investigations :

FBS

TGL

HDL

MASTER CHART

MetS subjects:

NAME	AGE	SEX	BMI	WC	FBS	TGL	HDL	SBP	DBP	TSH
SUBHA	32	F	26	92	104	162	50	110	74	5.9
MYMOON	29	F	26.4	96	98	188	40	126	80	7.4
DURATCHI	47	F	28.4	102	110	210	45	140	90	9.1
STELLA	36	F	26.3	94	97	174	54	135	95	7
ESWARI	46	F	26.2	90	102	162	44	130	85	8.4
STEFFI	28	F	25.3	92	89	198	47	124	70	7.7
GAYATHRI	38	F	23.9	89	108	172	52	116	76	6.8
CHELLAM	40	F	28.1	95	94	185	41	145	94	9.2

RIYANA	45	F	25.3	90	115	202	46	130	78	8.1
JEYA	46	F	25.9	90	104	230	43	140	90	6.4
NANDHINI	29	F	26.4	92	92	162	48	126	87	5.9
HELEN	37	F	28.1	95	88	171	47	124	78	9.2
ALAGU	39	F	26.4	88	108	167	42	130	85	7.1
ZAHIDHA	40	F	24.9	95	94	178	39	140	82	8.2
DHANAM	44	F	27.4	97	97	182	52	140	90	8.7
GNANAM	32	F	30.2	101	90	190	44	118	90	7.6
MANGAI	38	F	26.9	93	102	165	41	134	92	7.2
KRISHNAN	38	M	28.4	102	98	185	39	135	90	7.6
ASHWIN	28	M	25.3	95	100	170	37	130	82	6.8
SRIDHAR	33	M	29.4	104	104	192	35	135	92	9.2
SUBRAMANI	40	M	24.3	99	96	164	40	140	90	8.8
SHANTHI	38	F	23.8		101	138	40	127	76	3.2
MALLIGA	42	F	24.6	90	95	142	42	138	90	3.7
LAKSHMI	36	F	24.2	83	110	122	45	130	80	2.2
JEYA	28	F	25	87	98	152	47	120	88	4.2
ALAGAMMAL	39	F	24.3	90	104	145	47	130	90	2.5
MENAKA	44	F	23.8	92	97	121	42	140	86	3.6
GOMATHI	38	F	26	87	92	137	41	135	92	4.5
KARPAGAM	40	F	25.6	88	108	143	55	140	90	4
JEBA	46	F	24.7	82	102	150	52	144	90	2.4
PRINCY	32	F	23.9	84	105	128	51	138	88	2.8
GEETHA	39	F	25.2	88	102	143	55	136	92	3.2
LAVANYA	35	F	26.8	89	89	110	47	140	95	3.4
MANGAMMAL	45	F	25.9	91	102	154	58	135	88	2.1
SELVI	26	F	22.9	83	88	138	41	130	92	3.7
PREMA	48	F	23.7	82	92	120	42	144	96	3.1
LALITHA	41	F	24.1	84	103	118	48	126	80	4.8
FATHIMA	28	F	23.8	85	95	145	42	135	88	4.2
DHIVYA	30	F	25.1	90	102	155	47	127	82	2.6
ARASI	39	F	23.8	85	88	162	49	120	90	2.3
POONKODI	42	F	24.7	82	100	142	48	138	86	3.6
PACKIAM	37	F	25.2	88	94	174	54	146	92	4.1
PETCHI	40	F	23.3	84	110	124	46	135	80	4.3
LAKSHMI	36	F	26.7	91	96	139	48	136	90	4.2
MARIAMMAL	32	F	25.9	85	102	148	41	110	70	3.7
NAGALAKSHMI	38	F	26.2	87	110	146	50	124	90	3.5

ESAKKI	33	F	23.7	84	102	137	48	108	70	2.1
PANDEESWARI	37	F	25.4	88	98	124	46	136	92	2.7
DURGA	42	F	23.6	81	88	117	42	140	88	2.4
ANDAL	41	F	25.8	87	98	149	44	130	90	3.5
FLORA	32	F	26.8	89	102	157	54	112	76	3.2
KALYANI	33	F	23.5	83	89	146	43	138	88	4.8
PRIYA	31	F	29.6	98	89	182	47	130	87	3.4
SEETHA	35	F	27.3	91	104	132	44	124	80	3.8
AISHWARYA	26	F	25.8	92	98	146	44	128	88	4.7
SASIKALA	35	F	27.9	94	87	134	44	126	88	2.4
RAJESWARI	38	F	25.7	89	105	129	54	138	86	2.9
THILAGAM	39	F	23.9	87	98	167	54	140	92	4.2
MARY	37	F	27.2	93	110	138	42	110	70	3.7
SUSEELA	34	F	24.7	92	85	125	38	130	92	3.1
BHANU	33	F	25.3	89	102	118	48	138	84	1.9
KALIAMMAL	38	F	24.1	83	84	116	42	144	88	2.6
PASUVATHI	42	F	24.8	85	115	142	52	150	86	4.2
VANI	29	F	25.6	88	96	158	39	122	74	1.8
ESWARI	39	F	27.1	92	108	146	43	110	70	4.3
RAM KUMAR	36	M	28.4	94	98	125	36	124	90	3.7
SARAVANAN	38	M	26.5	93	89	137	32	126	86	3.4
ALEX	40	M	26.3	97	110	148	37	126	74	2.9
FAKRUDEEN	42	M	27.1	98	85	160	33	128	84	2.2
MANIKANDAN	37	M	26.5	92	82	139	36	128	90	2.6
KARUPPIYAH	44	M	27.2	96	92	128	38	128	92	1.8
KATHIR	28	M	29.4	105	98	148	35	128	88	3.2
RAHMAN	34	M	28.3	97	87	155	39	130	82	3.7
PANDIAN	38	M	26.4	92	104	130	44	130	94	2.8
RAJA	32	M	26.9	97	98	117	32	134	90	2.6
ALAGAR	41	M	27.4	93	89	152	36	136	84	4.7
RANGASAMY	46	M	29.1	99	102	149	38	136	88	3.9
BRITTO	36	M	26.3	94	82	137	36	136	82	4.2
BALAJI	32	M	26.1	92	94	126	32	136	95	1.5
SAMPATH	40	M	27.8	100	92	158	43	136	94	2.9
DURAI	31	M	27.4	98	98	160	36	136	86	2.4
GANAPATHY	37	M	27.3	99	110	145	38	138	82	3.5
MOHAMMED	42	M	28.4	93	84	142	38	138	96	4.1

VENKATACHALAM	48	M	26.8	97	102	137	37	138	80	3.8
ESAKKI	39	M	27.6	95	88	128	38	138	100	3.2
JOHNSON	38	M	29.8	98	92	126	34	138	94	2.5
VADIVEL	41	M	25.7	93	98	115	32	138	96	1.9
NARAYANAN	34	M	25.3	96	90	140	37	138	92	2.3
MUTHUSAMY	31	M	26.1	94	97	138	33	140	90	2
KUMAR	39	M	26.8	92	115	123	38	140	84	4.3
PANDY	41	M	24.9	94	98	156	44	140	96	3.9
VISHNU	29	M	24.6	91	89	144	33	142	88	2.9
SHIVA	38	M	26.7	101	106	115	32	142	90	3.6
JERRY	32	M	23.1	92	102	150	36	142	88	4.5
SURULI	30	M	27.4	96	92	146	36	142	84	4.1
VIGNESH	37	M	23.8	93	105	132	31	144	84	2.1
MOHAN	41	M	26.7	98	98	152	38	144	82	1.8
BALACHANDAR	39	M	26.3	95	88	117	36	145	98	2.3
CHANDRAN	33	M	25.8	92	102	145	34	146	82	3.7
PRABHU	36	M	28.4	98	88	160	38	150	80	4.1

Controls:	age	sex	BMI	waist circumference	FBS	TGL	HDL	SBP	DBP	TSH
PALANIAMMAL	38	F	21.6	76	80	115	49	110	78	2.4
SHEEBA	27	F	20.7	78	90	120	52	124	80	3.6
NAGU	29	F	21.4	74	87	122	55	128	78	3.8
SUBHASREE	34	F	19.9	79	91	105	48	130	82	4.4
VASUKI	37	F	22.2	80	92	132	52	110	78	2.1
ANU	31	F	20.5	77	90	115	50	120	80	1.9
KOTHAI	40	F	23.9	82	92	164	52	120	82	7.2
THILAGAVATHI	36	F	19.4	74	96	108	47	114	78	4.2
SUDHA	33	F	21.3	79	88	118	43	114	80	3.9
GOLDY	29	F	20.6	72	90	127	54	126	82	3.3
KALYANI	41	F	22.8	78	87	109	53	130	80	3.5
MANGAI	43	F	20.7	81	84	128	49	110	74	2.8
SUSEELA	38	F	19.6	73	97	110	50	120	76	2.5
KARTHIGA	35	F	23.4	76	83	128	53	130	78	3.9
LATHA	26	F	24.2	84	88	159	51	110	78	6.8
SOUNDHARYA	30	F	21.2	75	92	145	47	126	78	4.7
KALISWARI	36	F	22.1	80	85	98	46	124	84	4.2
AVUDAIAMMAL	38	F	19.8	71	90	132	51	128	76	3.9
VANITHA	31	F	22.7	77	82	104	47	114	74	2.2
VIJAYA	33	F	20.5	75	86	123	48	124	76	1.9
ULAGAMMAL	30	F	21.8	73	88	108	49	110	74	4.2

SAROJA	29	F	22.4	79	91	117	54	124	78	4.6
KOKILA	34	F	21.3	74	84	105	51	118	80	4.1
RADHA	38	F	23.2	82	89	126	49	114	78	2.9
PERIANAYAGI	36	F	22.8	76	82	145	52	120	84	3.9
ARUMUGAM	28	M	23.1	84	84	130	44	128	84	3.2
PRAKASH	32	M	19.8	82	88	124	42	116	78	2.9
VELAN	39	M	18.7	80	90	115	40	118	82	3.7
KINGSLY	31	M	22.1	84	92	132	39	124	76	3.2
RAJESH	40	M	20.7	88	90	112	41	130	82	1.2
SUNDARAM	45	M	19.4	82	94	108	37	126	82	1.7
SRIDHARAN	38	M	23.9	90	96	172	42	124	80	7.3
ARAVIND	29	M	20.1	86	88	132	44	116	76	3.9
BARANI	33	M	22.1	82	81	107	42	112	70	4.2
GUNAALAN	38	M	21.4	85	86	98	42	124	74	3.8
MUTHURAJ	40	M	21.9	88	94	132	38	114	74	2.7
SUDALAI	35	M	19.9	81	78	121	36	120	80	2.4
KUMARESAN	33	M	20.7	82	83	116	43	116	82	1.9
SYED IBRAHIM	44	M	20.5	86	96	104	41	126	82	3.8
KARTHIKEYAN	39	M	22.4	83	91	128	40	122	76	4.4
KOMBAIYAH	41	M	21.5	82	90	110	39	122	82	4.6
ARUL	26	M	21.9	81	79	98	41	110	70	3.5
RAMAN	36	M	20.5	80	86	124	44	116	76	3.3
LINGAM	42	M	22.7	91	81	142	41	132	84	3.8
VIJAYAN	31	M	21.3	89	89	136	39	120	78	1.5
THANGASAMY	38	M	23.5	92	94	118	37	118	74	1.8
PRABHU	28	M	21.5	84	86	109	44	130	90	4.1
MAHESH	35	M	20.2	82	92	132	42	124	72	2.7
ANBU	28	M	19.6	80	90	142	41	128	78	2.8
RAJESH	45	M	20.6	81	94	139	47	124	80	3.3